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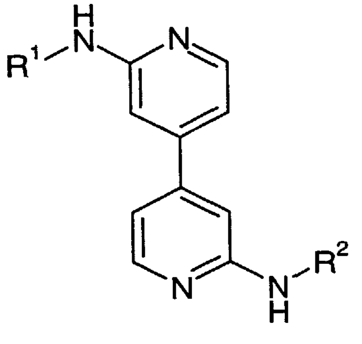
(54) Title: PYRIDINE DERIVATIVES AS JNK INHIBITORS AND THEIR USE



(I)

(57) Abstract: The present invention relates to new compounds of formula (I) whrein: R^1 is aryl or heteroaryl, each of which is optionally substituted with one or more of R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halogeno or NO_2; R^2 is R^5, R^6, COR^5, COR^6, $CONHR^5$, $CONHR^6$, $CON(R^6)_2$, $COOR^5$, $COOR^6$, SO_2R^5 or SO_2R^6; a process for their preparation and new intermediates used therein, pharmaceutical formulations containing said therapeutically active compounds and to the use of said active compounds in therapy.

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Pyridine derivatives as JNK inhibitors and their use

TECHNICAL FIELD

The present invention relates to novel pyridine derivatives, useful for treatment of various disorders. The invention relates to methods for producing these compounds. The invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of utilizing these compositions in the treatment of various disorders.

BACKGROUND TO THE INVENTION

Protein kinases are important components of intracellular signalling pathways and kinases are involved in the regulation of a variety of cellular functions. The MAP kinase signalling pathways are activated by engagement of a number of cell surface receptors. One of these pathways, the JNK pathway is activated specifically by stress or pro-inflammatory cytokines. Activators include LPS, the cytokines tumor necrosis factor (TNF-α) and Interleukin-1 (IL-1), osmotic shock, chemical stress and UV radiation (Cohen, P. Trends in Cell Biol. 7:353-361 1997). Targets of the JNK pathway include a number of transcription factors, such as but not exclusively c-jun and ATF-2 (Whitmarsh, A. and Davis, R. J. Mol. Med. 74:589-607 1998).

Three different genes: JNK1, JNK2 and JNK3; encode the JNK family of enzymes. Alternatively spliced forms of these genes can give rise to 10 distinct isoforms: four for JNK1, four for JNK2 and two for JNK3. (Gupta, S. et al EMBO J. 15:2760-2770 1996). JNK1 and JNK2 are ubiquitously expressed in human tissues whereas JNK3 is selectively expressed in the brain, heart and testis (Dong, C. et al. Science 270:1-4 1998).

JNKs 1, 2 and 3 have been selectively knocked out in mice both singularly and in combination by both gene deletion and/or transgenic expression of dominant negative forms of the kinases (Dong, C. et al Science 282:2092-2095, 1998; Yang, D. et al Immunity 9:575-585 1998; Dong, C., et al Nature 405:91-94 2000; Yang, D. et al Nature 389:865-870 1997). Mice with targeted disruption of the JNK3 gene develop normally and are protected from excitotoxin-induced apoptosis of neurons. This finding suggests that specific inhibitors of JNK 3 could be effective in the treatment of neurological disorders characterized by cell death such as Alzheimer's disease and stroke. Mice disrupted in either JNK 1 or 2 also develop normally. Peripheral T cells from either type of mice can be activated to make IL2, but in both cases, there is a defect in Th1 cell development. In the case of JNK1 -/- mice, this is due to an inability to make gamma interferon (a key cytokine essential for the differentiation of Th1 cells). In contrast, JNK2 -/- mice produce interferon gamma but are unable to respond to the cytokine. Similar defects in T cell biology (normal IL2 production but a block in Th1 cell differentiation) are seen in T cells disrupted in the MKK7 gene confirming this role for the JNK pathway in T cell differentiation (Dong, C., et al Nature 405:91-94 2000).

JNK also plays a major role in apoptosis of cells (Davis RJ. Cell. 103:239-252, 2000). JNK is essential for UV induced apoptosis through the cytochrome C mediated pathway (Tournier, C. et al Science 288:870-874 2000). Ischemia and ischemia coupled with re-perfusion as well as restricted blood flow itself have been shown to be accompanied by activation of JNK. Cell death can be prevented with dominant negative forms of JNK transfected into cells demonstrating a potential utility for JNK in conditions characterized by stress-induced apoptosis.

Activation of the JNK pathway has been observed in a number of human tumors and transformed cell lines (Davis RJ. Cell. 103:239-252, 2000). Indeed, one of the major targets of JNK, c-jun, was originally identified as an oncogene indicating the potential of this pathway to participate in unregulated cell growth. JNK also regulates phosphorylation of p53 and thus modulates cell cycle progression (Chen T. et al Mol. Carcinogenesis 15:215-226, 1996). Inhibition of JNK may therefore be beneficial in some human cancers.

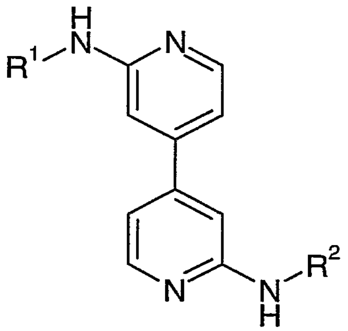
Based on current knowledge JNK signalling, especially JNK3, has been implicated in areas of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, Huntington's disease, traumatic brain injury, as well as ischemic and haemorrhaging stroke.

Thus there is a high unmet medical need for JNK specific inhibitors useful in treating the various conditions associated with JNK activation.

DISCLOSURE OF THE INVENTION

It has been found that compounds of the Formula **I**, which are substituted pyridine compounds, are particularly effective and thereby suitable in the treatment of the various conditions.

In one aspect, the invention relates to compounds of the general Formula **I**



(I)

wherein:

R^1 is aryl or heteroaryl, each of which is optionally substituted with one or more of R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halogeno and NO_2;

R^2 is R^5, R^6, COR^5, COR^6, $CONHR^5$, $CONHR^6$, $CON(R^6)_2$, $COOR^5$, $COOR^6$, SO_2R^5 or SO_2R^6;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} trifluoroalkoxyl;

R^5 is aryl or heteroaryl, each of which is optionally substituted with one or more of R^7, OR^7, $OCOR^7$, $COOR^7$, COR^7, $CONR^7R^8$, $CONHOR^7$, $NHCOR^7$, NR^7R^8, $NHSO_2R^7$, SO_2R^7, $SO_2NR^7R^8$, SR^7, R^7SR^8, CN, halogeno, oxygen and NO_2;

R^6 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, heteroarylC_{1-6} alkyl, arylC_{1-6} alkyl, C_{1-6} alkoxyl, or C_{2-6} alkenyl, wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, heteroarylC_{1-6} alkyl, arylC_{1-6} alkyl, C_{1-6} alkoxyl and C_{2-6} alkenyl is optionally substituted with one or more A;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heteroarylC_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, aryl, C_{1-6} fluoroalkyl and C_{1-6} chloroalkyl,wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heteroaryl, heteroarylC_{1-6} alkyl, heterocycle and heterocycleC_{1-6} alkyl is optionally substituted with one or more B;

R^9 and R^{10} are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heterocycle, heterocycleC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6} alkyl, aryl or arylC_{1-6} alkyl, wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heterocycle, heterocycleC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6} alkyl, aryl or arylC_{1-6} alkyl is optionally substituted with one or more B;

A is R^9, OR^9, $OCOR^9$, $COOR^9$, COR^9, $CONR^9R^{10}$, $CONHOR^9$, $NHCOR^9$, NR^9R^{10}, $NR^9SO_2R^{10}$, SO_2R^9, $SO_2NR^9R^{10}$, SR^9, R^9SR^{10} ,CN or halogeno;

B is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino or halogeno;

as a free base or a salt, solvate or solvate of salt thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups. C_{1-6}alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, and hexyl.

In this specification, unless stated otherwise, the term "C_{3-8} cycloalkyl" includes a non-aromatic, completely saturated cyclic aliphatic hydrocarbon group containing 3 to 8 atoms. Examples of said cycloalkyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "alkoxyl" as used herein, unless stated otherwise includes "alkyl"O groups in which "alkyl" is as hereinbefore defined. C_{1-6}alkoxyl may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy, hexyloxy. C_{1-6} trifluoroalkoxyl represents a C_{1-6} alkoxyl substituted with three fluorine atoms.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl is specific for the straight chain version only. Unless otherwise stated, the term "alkenyl" advantageously refers to chains with 2 to 5 carbon atoms, preferably 3 to 4 carbon atoms. C_{2-6}alkenyl may be ethenyl, propenyl, 2-methylpropenyl, butenyl and 2-butenyl.

In this specification, unless stated otherwise, the term “alkynyl” includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl is specific for the straight chain version only. Unless otherwise stated, the term “alkynyl” advantageously refers to chains with 2 to 5 carbon atoms, preferably 3 to 4 carbon atoms.

In this specification, unless stated otherwise, the term “heterocycle” includes a 3- to10-membered non-aromatic partially or completely saturated hydrocarbon group, which contains one or two rings and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl, tetrahydropyranyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term “aryl” may be a C_6– C_{14} aromatic hydrocarbon and includes, but is not limited to, benzene, naphthalene, indene, anthracene, phenanthrene.

In this specification, unless stated otherwise, the term “heteroaryl” may be a monocyclic heteroaromatic, or a bicyclic fused-ring heteroaromatic group. Examples of said heteroaryl include, but are not limited to, pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, benzofuryl, 4-oxo-4,5,6,7-tetrahydro-1-benzofuryl, indolyl, isoindolyl, benzimidazolyl, 2-oxobenzoxazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl or triazolyl.

In this specification, unless stated otherwise, the term halogeno may be fluor, chlorine, bromine or iodine.

In this specification, unless stated otherwise, the term “C_{1-6} fluoroalkyl” may be an alkyl substituted with one or more fluorine atoms. Examples of said fluoroalkyl include, but are not limited to, monofluoromethyl, trifluoromethyl, difluoromethyl and trifluoroethyl.

In this specification, unless stated otherwise, the term "C_{1-6} chloroalkyl" may be an alkyl substituted with one or more chlorine atoms. Examples of said chloroalkyl include, but are not limited to, monochloromethyl, trichloromethyl, dichloromethyl and trichloroethyl.

In one aspect of the present invention, there is provided a compound of formula **I**, wherein R^1 is aryl or heteroaryl, optionally substituted with one or more of R^3, OR^3, NR^3R^4, halogeno or NO_2;

R^2 is R^5, R^6, COR^5, COR^6, $CONHR^5$, $CONHR^6$, $COOR^6$ or SO_2R^6;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;

R^5 is aryl or heteroaryl each of which is optionally substituted with one or more of R^7, OR^7, $COOR^7$, COR^7, $CONHOR^7$, NR^7R^8, SO_2R^7, $SO_2NR^7R^8$, SR^7, halogeno, oxygen and NO_2;

R^6 is hydrogen, C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, wherein any of C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl or heterocycle is optionally substituted with one or more A;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocycle, wherein any of C_{1-6} alkyl is optionally substituted with one or more B;

R^9 and R^{10} are each independently hydrogen, or C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally substituted with one or more B;

A is $COOR^9$, COR^9, $CONR^9R^{10}$, $NHCOR^9$, NR^9R^{10}, SR^9, R^9SR^{10} , or CN;

B is halogeno or di(C_{1-6} alkyl)amino.

In another aspect of the present invention, there is provided a compound of formula **I**, wherein R^1 is aryl optionally substituted with one or more of R^3, OR^3 and NR^3R^4.

In one embodiment of this aspect there is provided a compound of formula **I**, wherein R^1 is aryl and said aryl is phenyl.

In yet another aspect of the present invention, there is provided a compound of formula **I**, wherein R^3 is selected from C_{1-6} fluoroalkyl, methyl and halogeno.

In yet another aspect of the present invention, there is provided a compound of formula **I**, wherein R^2 is selected from R^5, COR^5 and $CONHR^5$.

In one embodiment of this aspect there is provided a compound of formula **I**, wherein R^5 is aryl, optionally substituted with one or more of R^7, OR^7, $COOR^7$, COR^7, $CONHOR^7$, NR^7R^8, SO_2R^7, $SO_2NR^7R^8$, SR^7, halogeno, oxygen and NO_2.

In another embodiment of this aspect there is provided a compound of formula **I**, wherein R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocycle, wherein C_{1-6} alkyl is optionally substituted with one or more B, said B being halogeno.

In yet another aspect of the present invention, there is provided a compound of formula **I**, wherein R^2 is selected from R^6, COR^6, $CONHR^6$ and SO_2R^6.

In one embodiment of this aspect there is provided a compound of formula **I**, wherein R^6 is selected from hydrogen, C_{1-6} alkyl, $(C_{3-8}$ cycloalkyl$)C_{1-6}$ alkyl, heterocycle, heterocycleC_{1-6} alkyl, wherein any of C_{1-6} alkyl, $(C_{3-8}$ cycloalkyl$)C_{1-6}$ alkyl and heterocycle is optionally substituted with one or more A.

In another embodiment of this aspect there is provided a compound of formula **I**, wherein said A is selected from $COOR^9$, COR^9, $CONR^9R^{10}$, $NHCOR^9$, NR^9R^{10}, SR^9, R^9SR^{10} and CN; and R^9 and R^{10} are each independently hydrogen or C_{1-6} alkyl.

The present invention relates to the use of compounds of formula **I** as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula **I**. Such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically-acceptable salt of a compound of Formula **I** is, for example, an acid-addition salt of a compound of Formula **I** which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric; or, for example a salt of a compound of Formula **I** which is sufficiently acidic, for example an alkali or alkaline earth metal salt, or a salt with an organic base.

Thus, in another embodiment of the present invention there is provided a compound of formula **I** in the form of a pharmaceutically acceptable salt.

Some compounds of formula **I** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers.

Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

Specific compounds of Formula **I** are:
N,N'-Bis[4-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(3,4-difluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis[3-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis[3-(trifluoromethoxy)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-fluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-methylphenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-aminophenyl)-4,4'-bipyridine-2,2'-diamine;

N,N'-Bis(2-methoxyphenyl)-4,4'-bipyridine-2,2'-diamine;

N,N'-Bis(2-ethoxyphenyl)-4,4'-bipyridine-2,2'-diamine;

N-(2'-anilino-4,4'-bipyridin-2-yl)-*trans*-4-methoxycyclohexanecarboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-*cis*-4-methoxycyclohexanecarboxamide;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*trans*-4-methoxycyclohexanecarboxamide;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*cis*-4-methoxycyclohexanecarboxamide;

N-(6-methylpyridin-2-yl)-*N'*-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-*N'*-pyridin-2-yl-4,4'-bipyridine-2,2'-diamine;

N-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-*N'*-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyridin-3-yl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyrimidin-2-yl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyrimidin-5-yl-4,4'-bipyridine-2,2'-diamine;

(2E)-1-{4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]phenyl}-3-(dimethylamino)prop-2-en-1-one;

4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-pyrrolidin-1-ylethyl)benzenesulfonamide;

4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-morpholin-4-ylethyl)benzenesulfonamide;

N-{4-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl}-N'-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyridin-4-yl-4,4'-bipyridine-2,2'-diamine;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-piperidin-1-ylpropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1,2,3-thiadiazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)isoxazole-5-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyrazine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-imidazole-4-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-furamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxybenzamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-bromo-2-furamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-(methylthio)nicotinamide;
Methyl 4-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}benzoate;
3-(acetylamino)-N-(2'-anilino-4,4'-bipyridin-2-yl)benzamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-[(pyridin-2-ylthio)methyl]-2-furamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide 1-oxide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-3-hydroxypyridine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-6-bromopyridine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)isonicotinamide 1-oxide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-hydroxynicotinamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-6-hydroxypyridine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-3-benzoylpyridine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-6-methylpyridine-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-3,5-dimethylisoxazole-4-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-methoxynicotinamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methyl-1,2,3-thiadiazole-5-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloroisonicotinamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-4-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methylisoxazole-4-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-pyrrole-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloronicotinamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-chloro-1H-indole-2-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-4-chloro-1H-pyrazole-3-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methyl-1H-pyrazole-3-carboxamide;
(2E)-N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(3-furyl)acrylamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanamide;
N'-(2'-anilino-4,4'-bipyridin-2-yl)-N,N-dimethylsuccinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-[(4-chlorophenyl)sulfonyl]acetamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxycyclohexanecarboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)butanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylpyrazine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-*N*'-phenylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-phenylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[1-(4-bromophenyl)ethyl]urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-thien-3-ylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(chloromethyl)phenyl]urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dimethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dimethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-ethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-fluoro-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-difluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-difluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorobenzyl)urea;
N-(4-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea;
N-(3-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-isopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-ethyl-6-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-mesitylurea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-propylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(dimethylamino)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-1,3-benzodioxol-5-ylurea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxy-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxy-5-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxybenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-nitrophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-nitrophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(methylthio)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(methylthio)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylbenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chloro-5-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-fluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3,4-trifluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropyl-6-methylphenyl)ure
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-tert-butylphenyl)urea;
Methyl 4-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)be
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dimethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-methoxyphenyl)urea
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(difluoromethoxy)phenyl]urea
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[2-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-bromo-3-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-dichloropyridin-4-yl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butyl-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[5-methyl-2-(trifluoromethyl)-3-f
ethyl 3-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)benzo
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-diisopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylbenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)u
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-{4-[(trifluoromethyl)thio]phenyl}
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3,5-bis(trifluoromethyl)phenyl]u
1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide;

N^3-acetyl-N^1-(2'-anilino-4,4'-bipyridin-2-yl)-β-alaninamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide;

3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)butanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-L-prolinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)acetamide;

Methyl 2'-anilino-4,4'-bipyridin-2-ylcarbamate;

N-(2'-anilino-4,4'-bipyridin-2-yl)methanesulfonamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)cyclohexanecarboxamide;

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-2-carboxamide;

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide;

Ethyl 4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-4-oxobutanoate;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-2-carboxamide;

(*S*)-3 *N*2-acetyl-*N*1-(2'-anilino-4,4'-bipyridin-2-yl)methioninamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

Ethyl 3-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-3-oxopropanoate;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(methylthio)propanamide;

(±)*N*-(2'-anilino-4,4'-bipyridin-2-yl)-2-pyrrolidin-2-ylacetamide;

(3*S*)-3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)-4-cyanobutanamide;

*N*1-(2'-anilino-4,4'-bipyridin-2-yl)cyclopropane-1,1-dicarboxamide;

(*3S*)-1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide (+) and (-);

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydrofuran-3-carboxamide;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydro-2*H*-pyran-4-carboxamide;

Ethyl 4-({2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoate;

4-({2'-[(4-Fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoic acid;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-3-(methylthio)propanamide;

(*±*)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;

(3*R*)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;

(3*S*)-1-acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;

1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}pyrrolidine-3-carboxamide;
3-(Aminosulfonyl)-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}benzamide;
Ethyl 2-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylate;
2-{[(2'-Anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylic acid;
N-phenyl-*N*'-(tetrahydro-2*H*-pyran-4-ylmethyl)-4,4'-bipyridine-2,2'-diamine;
N-phenyl-*N*'-(tetrahydrofuran-3-ylmethyl)-4,4'-bipyridine-2,2'-diamine;

as a free base or a salt, solvate or solvate of salt thereof.

The present invention relates to novel pyridine derivatives, which are inhibitors of c-Jun N-terminal kinases (JNKs). JNKs have been implicated in mediating a number of disorders. The invention relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing these compositions in the treatment of various disorders.

Pharmaceutical compositions

According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula **I**, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, for use in the prevention and/or treatment of conditions associated with c-Jun N-terminal kinases (JNKs).

The composition may be in a form suitable for oral administration, for example as a tablet, for parenteral injection as a sterile solution or suspension. In general the above compositions may be prepared in a conventional manner using pharmaceutically carriers or diluents. Suitable daily doses of the compounds of formula **I** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

A compound of formula **I**, or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof, can be used on its own but will usually be administered in the form of a pharmaceutical composition in which the formula I compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable diluent or carrier. Dependent on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), for example from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

A diluent or carrier includes water, aqueous polyethylene glycol, magnesium carbonate, magnesium stearate, talc, a sugar (such as lactose), pectin, dextrin, starch, tragacanth, microcrystalline cellulose, methyl cellulose, sodium carboxymethyl cellulose or cocoa butter.

A composition of the invention can be in tablet or injectable form. The tablet may additionally comprise a disintegrant and/or may be coated (for example with an enteric coating or coated with a coating agentsuch as hydroxypropyl methylcellulose).

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula **I**, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, a hereinbefore defined, with a pharmaceutically acceptable diluent or carrier.

An example of a pharmaceuticall composition of the invention is an injectable solution containing a compound of the invention, or a a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, and sterile water, and, if necessary, either sodium hydroxide or hydrochloric acid to bring the pH of the final composition to about pH 5, and optionally a surfactant to aid dissolution.

Liquid solution comprising a compound of formula **I**, or a salt thereof, dissolved in water.

Solution	mg/ml
Compound X	5.0% w/v
Pure water	To 100%

Medical use

The compounds of Formula **I** have activity as medicaments. In particular the compounds of formula **I** are potent JNK inhibitors and preferred compounds are selective JNK3 inhibitors. The present invention provides a compound of Formula **I** for use as a medicament. In particular the present invention provides a compound of Formula **I** for use in the prevention or treatment of conditions associated with JNK activation.

The present invention provides a method of treating or preventing conditions associated with JNK activation comprising the administration of a therapeutically effective amount of a compound of Formula **I** to a mammal (particularly a human including a patient) in need thereof.

In a further aspect the present invention provides the use of a compound of Formula **I** in the manufacture of a medicament for the treatment of conditions associated with JNK activation.

Conditions that may be treated by the compounds of this invention, according to Formula **I**, or a pharmaceutical composition containing the same, include any condition associated with JNK activation. Conditions associated with JNK activation include but are not limited to:

central or peripheral neurological degenerative disorders including Alzheimer's disease, cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, epilepsy, a peripheral neuropathy, spinal cord injury, head trauma;

autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, asthma, septic shock, transplant rejection;
cardiovascular diseases including stroke, arterosclerosis, myocardial infarction, myocardial reperfusion injury;
cancer including breast-, colorectal, pancreatic, prostate cancer.

In addition, JNK inhibitors of the instant invention may be capable of inhibiting the expression of inducible pro-inflammatory proteins. Therefore other conditions, which may be treated by the compounds of this invention, include edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain and arthritis pain.

In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The term "condition", unless stated otherwise, means any disorder and disease associated with JNK activity.

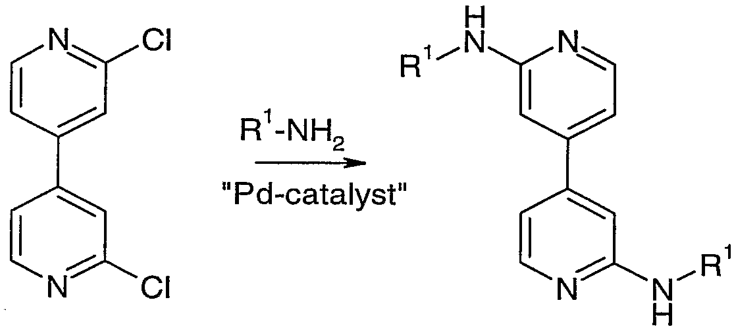
Non-medical use

In addition to their use in therapeutic medicine, the compounds of formula **I** or salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of JNK inhibitor related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Methods of preparation

The compounds of this invention may be prepared by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes and procedures below and by the preparative examples that follow. The starting material compounds are commercially available, unless otherwise stated.

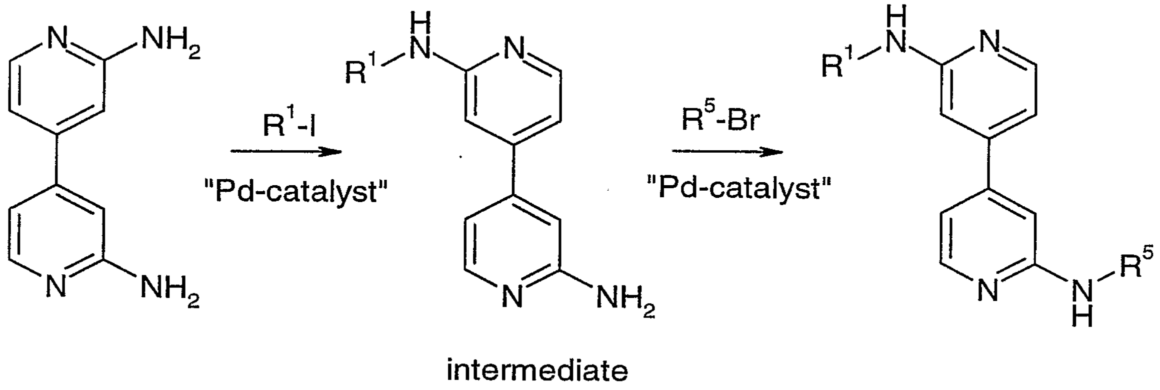
Synthetic scheme Method 1:



wherein R^1 is as described above.

In Method **1**, 2,2'-dichloro-(4,4')-bipyridine is reacted with an amine with a transition metal catalyst such as a palladium catalyst in an ether or hydrocarbon solvent to give a N,N'-bis-aryl-4.4'-bipyridine-2,2'-diamine. The reaction is carried out at elevated temperature such as 120°C for an extended time such as 15 hours or in a microwave oven at 160°C for a shorter time such as 1h. The reaction is monitored by chromatography until completion.

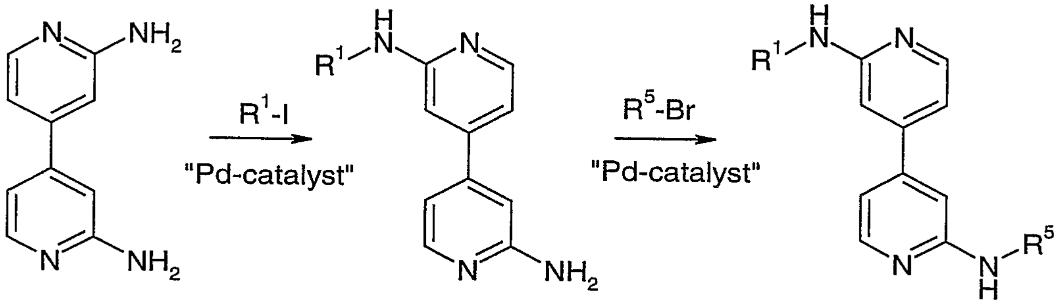
Synthetic scheme Method 2:



wherein R^1 and R^5 are as described above.

In Method **2**, 4.4'-bipyridine-2,2'-diamine is reacted with an arylhalide with a transition metal catalyst such as a copper or a palladium catalyst in the presence of a base such as sodium tert-butoxide (palladium) or potassium phosphate (copper) in an ether or hydrocarbon solvent to give an N-aryl-4.4'-bipyridine-2,2'-diamine (intermediate). The reaction is carried out at room temperature or at an elevated temperature such as 80 to 100°C for an extended time such as 15 hours or in a microwave oven at 160°C for a shorter time such as 1h. The reaction is monitored by chromatography until completion. After purification by chromatography the intermediate is subjected to a second arylation reaction to obtain a unsymmetrical N,N-diaryl-4.4'-bipyridine-2,2'-diamine.

Consequently, in one aspect of the present invention there is provided a process for the preparation of a compound of formula **Ia**, wherein R^1 and R^5 are as defined above;



II

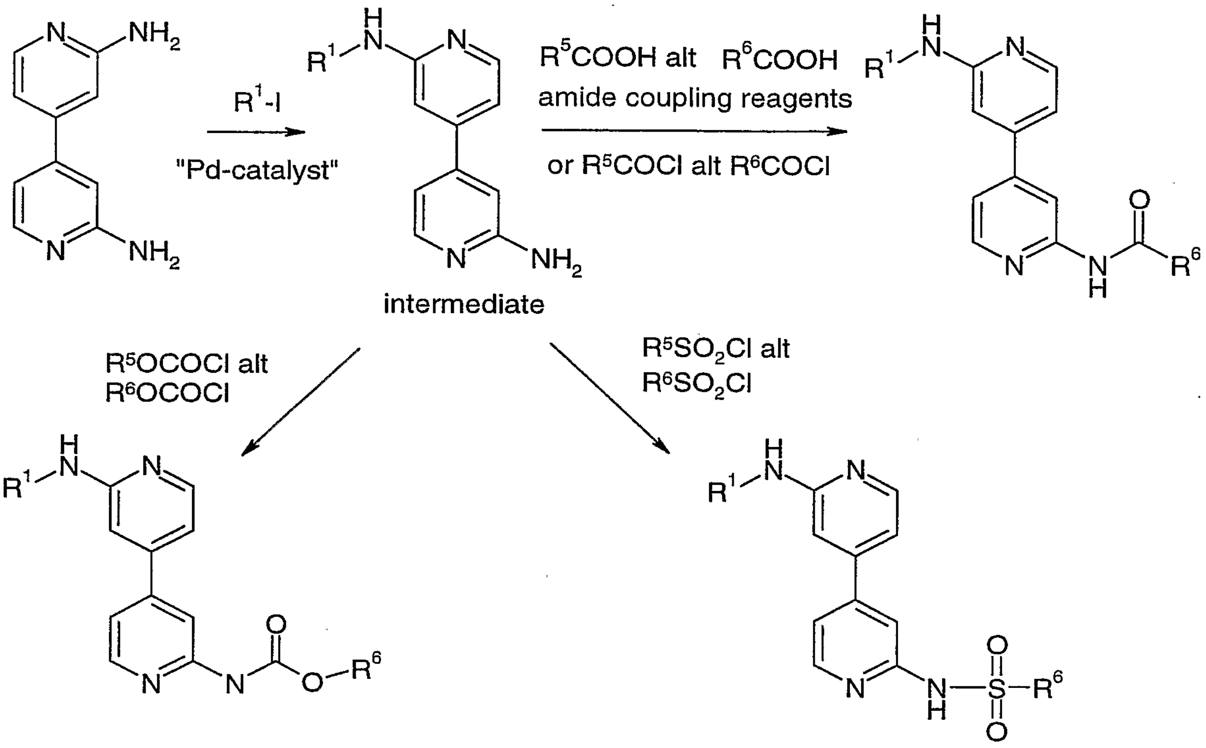
Ia

comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and

reacting a compound of Formula **II** in a second arylation reaction with an arylhalide (R^5-Br) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") to obtain a compound of formula **Ia**.

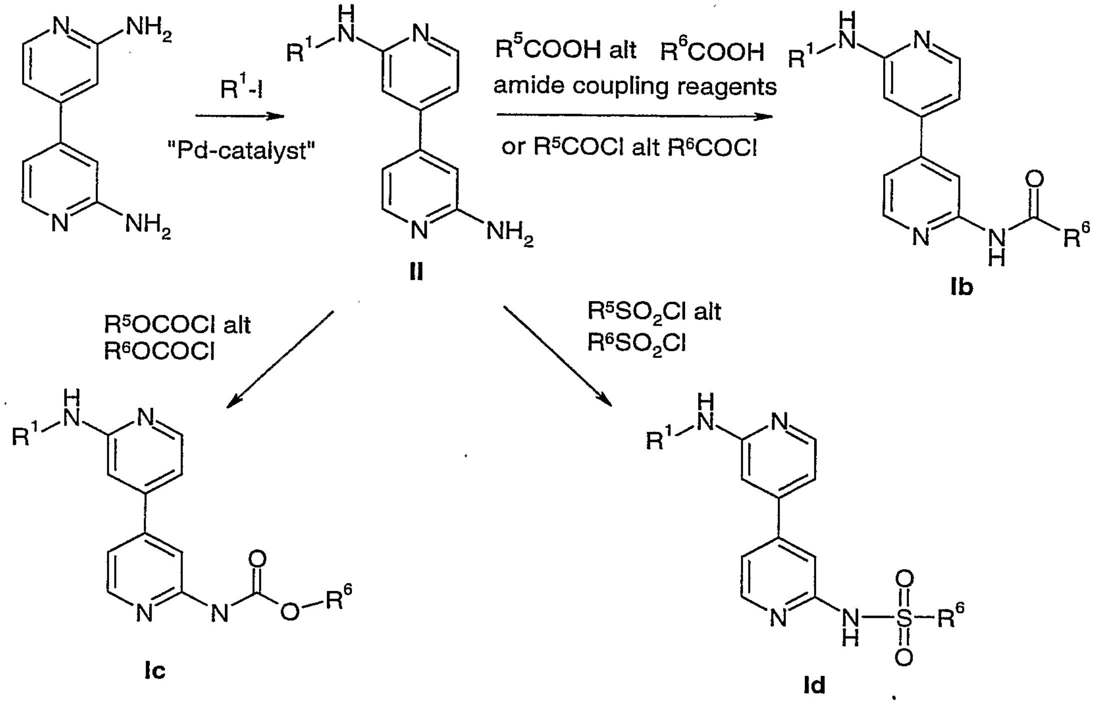
Synthetic scheme Method 3:



wherein R^1, R^5 and R^6 are as described above.

In Method **3**, the intermediate is reacted with a carboxylic acid in the presence of a peptide or amide coupling reagent such as TBTU and HOBt and a base such as diisopropylethylamine in an inert solvent such as DMF. The reaction is carried out at 25°C for a time of 1 to 8 days to give a carboxamide. Alternatively, the intermediate is reacted with a carboxylic acid chloride in an inert solvent such as dichloromethane in the presence of a base or in a solvent such as pyridine at 0 to 25°C for 1h to 12h to give a carboxamide. Analogously, carbamates and sulfonamides can be prepared from chlorocarbonates or sulfonylchlorides. The reaction is monitored by chromatography.

Consequently, in another aspect of the present invention there is provided a process for the preparation of a compound of formula **Ib**, **Ic** or **Id**, wherein R^1, R^5 and R^6 are as defined above;



comprising the steps:

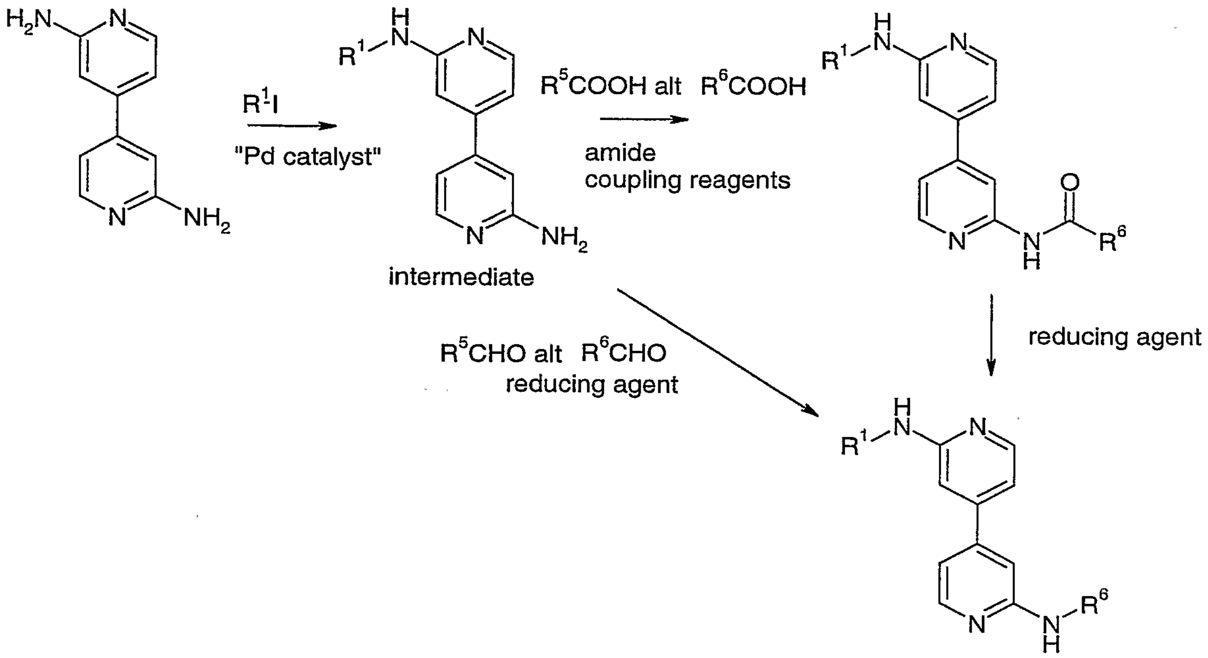
reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and

reacting said compound of Formula **II** with a carboxylic acid ("R^5COOH alt R^6COOH") in the presence of a amide coupling reagent and a base in an inert solvent to obtain a compound according to formula **Ib**; or

reacting said compound of Formula **II** with a carboxylic acid chloride ("R^5OCOCl alt R^6OCOCl") in an inert solvent in the presence of a base in a solvent to obtain a compound according to formula **Ic**; or

reacting said compound of Formula **II** with a chlorocarbonate or sulfonylchloride ("R^5SO_2Cl or R^6SO_2Cl") to obtain a compound according to formula **Id**.

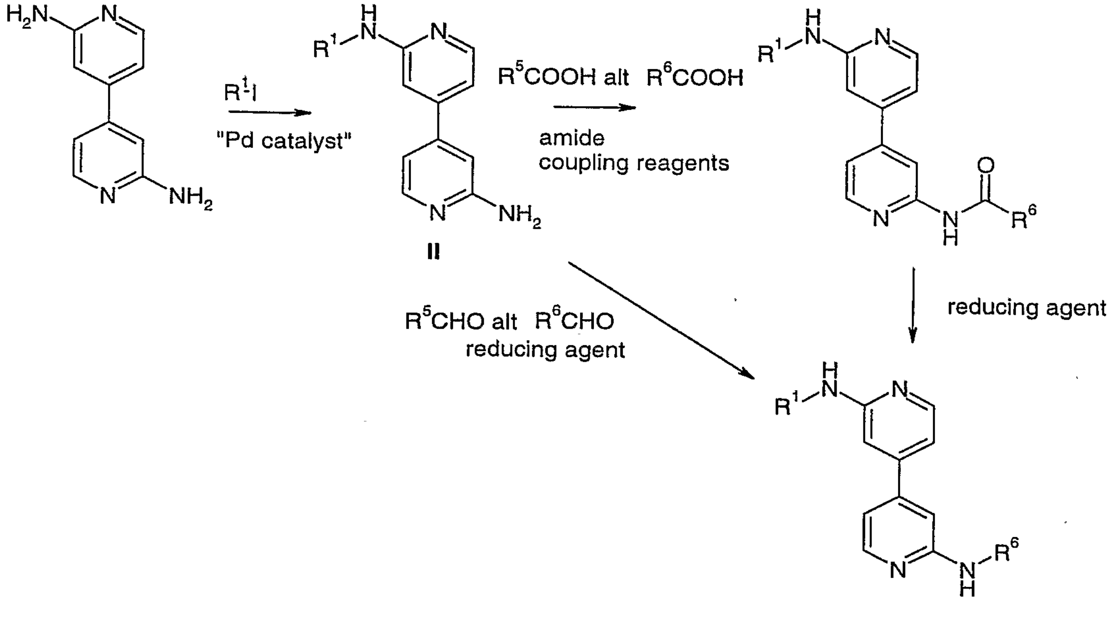
Synthetic scheme Method 4:



wherein R^1, R^5 and R^6 are as described above.

In Method **4**, the intermediate is reacted with a carboxylic acid as in Method 3 followed by reduction to the amine with a reducing agent such as lithium aluminium hydride or another hydride reagent in a solvent such as THF. The reaction is preferably carried out at elevated temperature such as 65°C for a time about 12 hours. Alternatively, the intermediate is reacted with a carboxaldehyde in the presence of a reducing agent such as a borohydride reagent. The reaction is carried out at a temperature such as 25°C for a time of about 12 hours.

Consequently, in another aspect of the present invention there is provided a process for the preparation of a compound of formula **Ie** wherein R^1, R^5 and R^6 are as defined above;



Ie

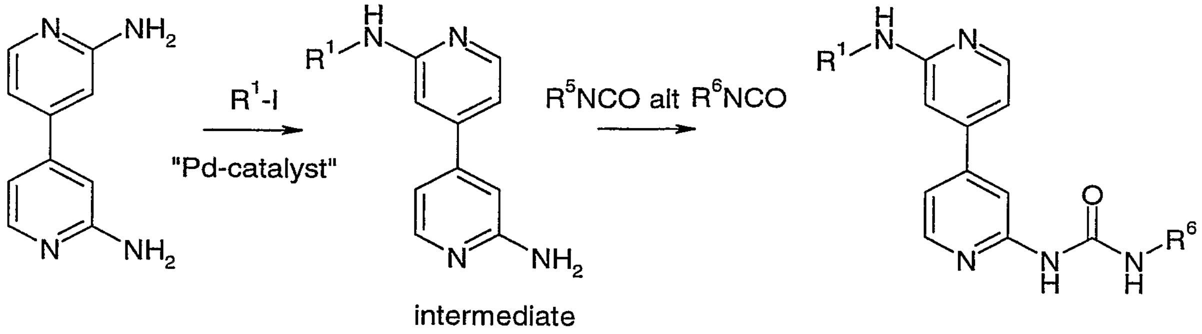
comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and

reacting said compound of Formula **II** with a carboxylic acid ("R^5COOH alt R^6COOH") followed by reduction to the amine with a reducing agent in a solvent to obtain a compound according to formula **Ie**; or

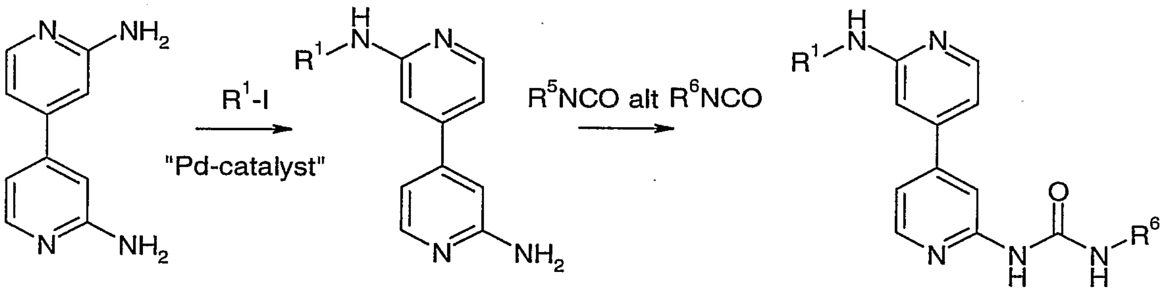
reacting said compound of Formula **II** with a carboxaldehyde ("R^5CHO alt R^6CHO") in the presence of a reducing agent to obtain a compound according to formula **Ie**.

Synthetic scheme Method 5:



In Method **5**, the intermediate is reacted with an isocyanate in a solvent such as dioxane. The reaction is preferably carried out at a temperature of 25°C for a time about 16 hours.

Consequently, there is provided a process for the preparation of a compound of formula **If**, wherein R^1, R^5 and R^6 are as defined above;

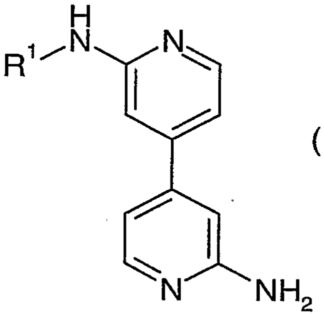


II **If**

comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and reacting said compound of Formula **II** with an isocyanate ("R^5NCO alt R^6NCO") in a solvent, to obtain a compound according to Formula **If**.

In another aspect the present invention provides a process for the preparation of a compound of Formula I comprising the reaction of a compound of Formula II:



(II)

wherein is R^1 is aryl or heteroaryl each of which is optionally substituted with one or more of the following R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halogeno or NO_2;

R^3 and R^4 are each independently hydrogen, halogeno, C_{1-6} alkyl, C_{1-6} alkyl optionally substituted by NR^3R^4, C_{3-8} cycloalkyl, C_{3-6} alkenyl, C_{3-6} alkenyl optionally substituted by NR^3R^4, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, hetrocycleC_{1-6} alkyl, C_{1-6} fluoroalkyl, or alternatively NR^3R^4 can form a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms being optionally substituted with one or more A;

A is C_{1-6} alkyl or halogeno;

as a free base or a salt, solvate or solvate of salt thereof.

Compounds of Formula II may be prepared as described in Methods 2 or 3.

Compounds of Formula II are novel, useful intermediates and are claimed as a further aspect of the present invention.

Compounds according to Formula II is exemplified by, but not limited to:
N-Phenyl-4,4'-bipyridine-2,2'-diamine;
N-(4-Fluorophenyl)-4,4'-bipyridine-2,2'-diamine;
as a free base or a salt, solvate or solvate of salt thereof.

WORKING EXAMPLES

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

All chemicals and reagents were used as received from suppliers. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a BRUKER DPX 400 (400 MHz) spectrometer using the following solvents and references.

$CDCl_3$: ^{1}H NMR TMS (0.0 ppm) and ^{13}C the central peak of $CDCl_3$ (77.0).

CD_3OD : ^{1}H NMR 3.31 ppm (central peak) and ^{13}C 49.0 ppm (central peak).

DMSO-d_6: ^{1}H NMR 2.50 ppm (central peak) and ^{13}C 39.51 ppm (central peak).

Mass spectra (TSP) were recorded on a Finigan MAT SSQ 7000 spectrometer.

Mass spectra (EI) were recorded on a Finigan MAT SSQ 710 spectrometer.

LC-MS were recorded on a Waters Alliance 2790 + ZMD spectrometer equipped with software Mass Lynx 3.5.

Flash column chromatography was carried out on silica gel 60 (230-400 mesh).

Example 1

_N,N'_-Bis[4-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine

(i) 2-Chloro-3-iodopyridine

2,2,6,6-tetramethylpiperidine (17 mL, 14 g, 0.1 mol) and 2-chloropyridine (9.5 mL, 11.5 g, 0.1 mol) were consecutively added at –78°C to n-butyllithium 1.6 M in hexanes (62.5 mL, 0.1 mol) in 150 mL of tetrahydrofuran. After 2h at -78°C, the mixture was treated with a solution of iodine (25.5 g, 0.1 mol) in THF (50 mL) and stirred for 30 min before being partitioned between water (100 mL) and diethyl ether (3 x 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium thiosulfate (2 x 50 mL),

dried over magnesium sulfate, filtered and concentrated under vacuum to afford a crude solid which was purified by flash chromatography (heptane/ethyl acetate 90/10). Yield: 72% (17.3 g), yellow solid. ^{1}H NMR (CDCl$_3$): δ 8.38 (dd, J = 4.6/1.7 Hz, 1H), 8.16 (dd, J = 8.0/1.6 Hz, 1H), 6.96 (dd, J = 8.0/4.6 Hz, 1H). ^{13}C NMR (CDCl$_3$): δ 154.5, 148.9, 148.8, 123.2, 94.9.
MS (EI) *m/z* 240 (M+1).

(ii) 2-Chloro-4-iodopyridine

A solution of 2-chloro-3-iodopyridine (12 g, 50 mmol) in 20 mL of THF was slowly added to a cold (-78°C) lithium diisopropylamide solution (prepared by the addition of n-butyllithium 1.6 M (31.25 mL, 50 mmol) in hexanes to a solution of diisopropylamine (7 mL, 50 mmol) in THF (100 mL). After 3h, water (20 mL) was added to the mixture, which was extracted with ether (2 x 100 mL). The organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum (20°C) to afford a brown solid, which was purified by filtration over silica (ethyl acetate/heptane 8/2). Yield: 95% (11.4 g), pale yellow needles. ^{1}H NMR (CDCl$_3$): δ 8.07 (d, J = 5.3 Hz, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.59 (dd, J = 5.0 / 1.1 Hz, 1H). ^{13}C NMR (CDCl$_3$): δ 151.7, 149.6, 133.0, 131.5, 106.6.
MS (EI) *m/z* 240 (M+1).

(iii) 2,2'-Dichloro-(4,4')-bipyridine

n-Butyllithium 1.6M in hexanes (6.25 mL, 10.0 mmol) was slowly added to a cold (-78°C) solution of 2-chloro-4-iodopyridine (4.79 g, 20.0 mmol) in 200 mL of THF. After 20 min at -78°C, a solution of trimethyltin chloride (2.0 g, 10.0 mmol) in 10 mL of THF was added dropwise. After 30 min, the ice bath was removed and the mixture was allowed to reach room temperature. After 1h, water (10 mL) was added and the solution was extracted with ether (2 x 50 mL). The organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to afford an orange oil. This crude product was diluted with toluene (50 mL) and flushed with nitrogen for 10 min. Then tetrakis(triphenylphosphine)palladium (578 mg, 0.5 mmol) was added and the mixture was heated at 110°C for 3 days. The mixture was filtered at room temperature and the precipitate was washed with water (2 x 20 mL), heptane (3 x 30 mL) and dried under vacuum to afford a white solid. Yield: 53 % (1.20 g). ^{1}H NMR (CDCl$_3$): δ 8.55 (d, J = 5.1

Hz, 2H), 7.57 (d, J = 1.3 Hz, 2H), 7.45 (dd, J = 5.1/1.3 Hz, 2H). ^{13}C NMR (CDCl$_3$): δ 152.81, 150.71, 147.35, 122.14, 120.21.
MS (TSP) *m/z* 225, 227(M+1).

(iv) ***N,N'*-Bis[4-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine**

2,2'-Dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 4-trifluoromethylaniline (0.3 mL, 2.4 mmol) were flushed in a schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with ethyl acetate (5 x 10 mL) and water (3 x 5 mL). The organic layers were separated, dried over magnesium sulfate and filtered. Silica gel was added to the filtrate, the solvents were evaporated under vacuum and the crude product purified by flash chromatography (ethyl acetate/heptane 8/2) to afford the title compound 12 mg (19 %) as a yellow solid. ^{1}H NMR (DMSO-d$_6$): δ 9.72 (s, 2H), 8.36 (d, J = 5.2 Hz, 2H), 7.93 (d, J = 8.4 Hz, 4H), 7.62 (d, J = 8.5 Hz, 4H), 7.18 (s, 2H), 7.16 (d, J = 5.1 Hz, 2H). ^{19}F NMR (DMSO-d$_6$): δ -60.09 (s, 6F).
MS (TSP) *m/z* 475 (M+1).

Example 2

***N,N'*-Bis(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine**

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 4-fluoroaniline (0.3 mL, 3.1 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with ethyl acetate (5 x 10 mL) and water (3 x 5 mL). The resulting powder was dried under vacuum to yield 48 mg (59 %) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d$_6$): δ 9.46 (s, 2H), 8.23 (d, J = 5.3 Hz, 2H), 7.73 (m, 4H), 7.09 (m, 6H), 6.99 (dd, J = 1.0/5.3 Hz, 2H). ^{19}F NMR (DMSO-d$_6$): δ -123.27 (m, 2F).

Example 3

N,N'-Bis(3,4-difluorophenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 3,4-difluoroaniline (0.5 mL, 4.0 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with toluene (5 x 10 mL), water (3 x 5 mL) and dichloromethane (5 x 2 mL). The resulting powder was dried under vacuum to yield 35 mg (66%) of the title compound as a slightly brown solid. ^{1}H NMR (DMSO-d_6): δ 9.71 (s, 2H), 8.29 (d, J = 5.3 Hz, 2H), 8.07 (ddd, J = 7.8/6.4/1.9 Hz, 2H), 7.38-7.28 (m, 4H), 7.12 (s, 2H), 7.06 (d, J = 5.4 Hz, 2H). ^{19}F NMR (DMSO-d_6): δ -138.17 (m, 2F), -149.26 (m, 2F). MS (TSP) *m/z* 411 (M+1).

Example 4

N,N'-Bis[3-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 3-trifluoromethylaniline (0.5 mL, 4.0 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with toluene (5 x 10 mL), water (3 x 5 mL) and dichloromethane (5 x 2 mL). The resulting powder was dried under vacuum to yield 80 mg (76 %) of the title compound. ^{1}H NMR (DMSO-d_6): δ 9.86 (s, 2H), 8.34 (d, J = 5.3 Hz, 2H), 8.28 (s, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.51 (t, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.19 (s, 2H), 7.10 (dd, J = 5.4/1.5 Hz, 2H). ^{19}F NMR (DMSO-d_6): δ -61.57 (s, 6F). MS (TSP) *m/z* 475 (M+1).

Example 5

N,N'-Bis[3-(trifluoromethoxy)phenyl]-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (22.5 mg, 0.10 mmol), palladium acetate (3.0 mg, 0.013 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (7.05 mg, 0.013 mmol), sodium *tert*-butoxide (36 mg, 0.375 mmol) and 3-trifluoromethoxylaniline (0.5 mL, 3.1 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with toluene (5 x 10 mL), water (3 x 5 mL) and dichloromethane (5 x 2 mL). The resulting powder was dried under vacuum to yield 35 mg (70 %) of the title compound. ^{1}H NMR (DMSO-d$_6$): δ 9.75 (s, 2H), 8.34 (d, J = 5.3 Hz, 2H), 8.01 (s, 2H), 7.60 (d, J = 7.9 Hz, 2H), 7.38 (t, J = 8.3 Hz, 2H), 7.17 (s, 2H), 7.11 (d, J = 5.3 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H). ^{19}F NMR (DMSO-d$_6$): δ -56.80 (s, 6F).
MS (TSP) *m/z* 507 (M+1).

Example 6

N,N'-Bis(2-fluorophenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (22.5 mg, 0.10 mmol), palladium acetate (3.0 mg, 0.013 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (7.05 mg, 0.013 mmol), sodium *tert*-butoxide (36 mg, 0.375 mmol) and 2-fluorolaniline (0.5 mL, 5.2 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with water (3 x 5 mL) and ethyl acetate (5 x 2 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (heptane/ethyl acetate 7/3) to yield 19 mg (50 %) of the title compound. ^{1}H NMR (CDCl$_3$): δ 8.32 (d, J = 5.1 Hz, 2H), 8.05 (t, J = 8.1 Hz, 2H), 7.17-7.12 (m, 4H), 7.04-6.96 (m, 6H), 6.73 (bs, 2H). ^{19}F NMR (CDCl$_3$): δ -130.25 (m, 2F). ^{13}C NMR (CDCl$_3$): δ 155.93, 153.54 (d, J = 243.7 Hz), 148.99, 148.01, 128.60 (d, J = 10.5 Hz), 124.47 (d, J = 3.6 Hz), 122.84 (d, J = 7.4 Hz), 121.10, 115.40 (d, J = 19.5 Hz), 113.66, 106.96.
MS (TSP) *m/z* 375 (M+1).

Example 7

N,N'-Bis(2-methylphenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (22.5 mg, 0.10 mmol), palladium acetate (3.0 mg, 0.013 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (7.05 mg, 0.013 mmol), sodium *tert*-butoxide (36 mg, 0.375 mmol) and 2-methylaniline (0.5 mL, 4.0 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with water (3 x 5 mL) and ethyl acetate (5 x 2 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (heptane/ethyl acetate 1/1) to yield the title compound. ^{1}H NMR (DMSO-d_6): δ 8.31 (s, 2H), 8.14 (d, J = 5.3 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.4 Hz, 2H), 7.15 (t, J = 7.4 Hz, 2H), 6.99 (t, J = 7.6 Hz, 2H), 6.95 (s, 2H), 6.91 (d, J = 5.3 Hz, 2H), 1.98 (s, 6H).
MS (TSP) *m/z* 367 (m+1).

Example 8

N,N'-Bis(2-aminophenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 2-aminoaniline (144 mg, 1.33 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with ethyl acetate (5 x 10 mL), methanol (3 x 5 mL) and water (5 x 2 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (heptane/ethyl acetate 1/1) to yield 27 mg (33 %) of the title compound. ^{1}H NMR (MeOD-d_4): δ 8.05 (d, J = 5.4 Hz, 2H), 7.13 (dd, J = 7.7/1.2 Hz, 2H), 7.04 (td, J = 8.1/1.5 Hz, 2H), 6.88 (d, J = 1.2 Hz, 2H), 6.87 (dd, J = 3.2/1.5 Hz, 2H), 6.72 (td, J = 7.7/1.5 Hz, 2H), 6.69 (s, 2H). ^{13}C NMR (MeOD-d_4): δ 160.05, 149.75, 149.44, 144.75, 128.04, 127.93, 127.27, 119.78, 118.02, 112.81, 107.20.
MS (TSP) *m/z* 369 (M+1).

Example 9

N,N'-Bis(2-methoxyphenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 2-methoxyaniline (0.5 mL, 4.4 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with ethyl acetate (5 x 10 mL), methanol (3 x 5 mL) and water (5 x 2 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (heptane/ethyl acetate 8/2) to yield 40 mg (46 %) of the title compound. ^{1}H NMR (DMSO-d_6): δ 8.29-8.25 (m, 4H), 8.22 (d, J = 5.7 Hz, 2H), 7.35 (m, 2H), 7.02-7.01 (m, 4H), 6.96-6.88 (m, 4H), 3.85 (s, 6H).
MS (TSP) *m/z* 399 (M+1).

Example 10

N,N'-Bis(2-ethoxyphenyl)-4,4'-bipyridine-2,2'-diamine

2,2'-dichloro-(4,4')-bipyridine (50 mg, 0.22 mmol), palladium acetate (5.6 mg, 0.022 mmol), bis[tri-(*tert*-butyl)phosphine]palladium (12.5 mg, 0.022 mmol), sodium *tert*-butoxide (60 mg, 0.61 mmol) and 2-ethoxyaniline (0.5 mL, 3.3 mmol) were flushed in a Schlenk tube for 10 min with nitrogen. Then, 1 mL of dry dioxane was added, the tube sealed and the mixture stirred at 120°C for 15h. The mixture was then cooled to 20°C, filtered and the solid washed with ethyl acetate (5 x 10 mL), methanol (3 x 5 mL) and water (5 x 2 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (heptane/ethyl acetate 8/2) to yield 35 mg (37 %) of the title compound. ^{1}H NMR (DMSO-d_6): δ 8.22 (d, J = 4.9 Hz, 2H), 8.21 (m, 2H), 8.12 (s, 2H), 7.32 (s, 2H), 7.03 (dd, J = 5.4/1.2 Hz, 2H), 7.00 (dd, J = 7.9/1.9 Hz, 2H), 6.94-6.87 (m, 4H), 4.10 (q, J = 7.0 Hz, 4H), 1.36 (t, J = 7.0 Hz, 6H).
MS (TSP) *m/z* 427 (M+1).

Example 11

N-Phenyl-4,4'-bipyridine-2,2'-diamine

4,4'-bipyridine-2,2'-diamine (described in J.Org.Chem. 1997 vol. 62 p. 2774-2781) (744 mg, 4.0 mmol), iodobenzene (0.448 mL, 4.0 mmol),

tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (208 mg, 0.2 mmol), 1,1'-bis(diphenylphosphino)ferrocene (220 mg, 0.4 mmol) and sodium *tert*-butoxide (538 mg, 5.6 mmol) were flushed under nitrogen for 20 min. in a 100 mL round bottom flask. Then, 20 mL of dry DMF were added and the mixture stirred at 100°C for 15h. The mixture was cooled down to room temperature, filtered over a celite pad, silica gel was added to the filtrate and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (ethyl acetate/methanol/triethylamine 94/3/3) to yield 277 mg (26 %) of the title compound. ^{1}H NMR (DMSO-d$_6$): δ 9.16 (s, 1H), 8.22 (d, J = 5.3 Hz, 1H), 8.01 (d, J = 5.3 Hz, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.26 (t, J = 8.1 Hz, 2H), 7.03 (s, 1H), 6.94 (dd, J = 5.1/0.9 Hz, 1H), 6.89 (t, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.1/1.1 Hz, 1H), 6.68 (s, 1H), 6.10 (s, 2H). ^{13}C NMR (DMSO-d$_6$): δ 160.94, 157.00, 149.23, 148.60, 147.29, 146.65, 141.94, 129.04, 120.99, 118.54, 112.22, 109.86, 108.00, 105.23.
MS (TSP) *m/z* 263 (M+1).

Example 12

N-(4-Fluorophenyl)-4,4'-bipyridine-2,2'-diamine :

4,4'-bipyridine-2,2'-diamine (187 mg, 1.0 mmol), 4-fluoroiodobenzene (222 mg, 1.0 mmol), copper iodide (10 mg, 0.05 mmol), potassium phosphate (425 mg, 2.0 mmol), ethylene glycol (111 µL, 2.0 mmol), 2-propanol (1.0 mL) and dry dimethylformamide (1.0 mL) were flushed in a screw-capped test tube for 10 min with nitrogen. The tube was sealed and put into the microwave oven at 160°C for 1h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (4 x 5 mL). The organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum to afford a brown solid which was purified by flash chromatography (ethyl acetate/methanol/triethylamine 94/3/3) to yield 98 mg (35 %) of the title compound. ^{1}H NMR (DMSO-d$_6$): δ 9.17 (s, 1H), 8.20 (d, J = 5.3 Hz, 1H), 8.00 (d, J = 5.3 Hz, 1H), 7.70-7.68 (m, 1H), 7.11 (t, J = 8.8 Hz, 2H), 7.08 (s, 1H), 6.95 (dd, J = 5.3/1.4 Hz, 1H), 6.74 (dd, J = 5.2/1.5 Hz, 1H), 6.08 (s, 2H). ^{19}F NMR (DMSO-d$_6$): δ -123.25 (m, 1F).
MS (TSP) *m/z* 281 (M+1).

Example 13

N-(2'-anilino-4,4'-bipyridin-2-yl)-*trans*-4-methoxycyclohexanecarboxamide

Ethyldiisopropylamine (129 mg, 1.0 mmol) was slowly added to a solution of *N,N,N',N'*-tetramethyl-o-(benzotriazol-1-yl)uronium tetrafluoroborate (241 mg, 0.75 mmol), hydroxybenzotriazole (101 mg, 0.75 mmol) and 4-methoxycylohexanecarboxylic acid (78 mg, 0.5 mmol) in 3 mL of acetonitrile under nitrogen at 20 °C. After 5min, this solution was added to a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.5 mmol) in 2 mL of dimethylformamide under nitrogen. After 4 days of stirring, the reaction was quenched with a saturated aqueous solution of sodium hydrogencarbonate (5mL). The aqueous layer was extracted with dichloromethane. The organic layers were dried over magnesium sulfate, the solvent removed under reduced pressure to afford a crude product, which was purified by reversed phase chromatography to yield 6 mg of the title compound. ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 1H), 8.32 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 8.28 (d, J = 5.0 Hz, 1H), 7.42-7.34 (m, 4H), 7.23 (dd, J = 1.6/5.1 Hz, 1H), 7.10 (m, 2H), 7.01 (dd, J = 1.5/5.2 Hz, 1H), 6.89 (s, 1H), 3.38 (s, 3H), 3.19 (m, 1H), 2.29 (m, 1H), 2.20-1.89 (m, 3H), 1.75 (m, 1H), 1.64 (m, 2H), 1.30 (m, 2H).
MS (TSP) *m/z* 403 (M+1).

Example 14

N-(2'-anilino-4,4'-bipyridin-2-yl)-*cis*-4-methoxycyclohexanecarboxamide

Ethyldiisopropylamine (129 mg, 1.0 mmol) was slowly added to a solution of N,N,N',N'-tetramethyl-o-(benzotriazol-1-yl)uronium tetrafluoroborate (241 mg, 0.75 mmol), hydroxybenzotriazole (101 mg, 0.75 mmol) and 4-methoxycylohexanecarboxylic acid (78 mg, 0.5 mmol) in 3 mL of acetonitrile under nitrogen at 20 °C. After 5min, this solution was added to a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.5 mmol) in 2 mL of dimethylformamide under nitrogen. After 4 days of stirring, the reaction was quenched with a saturated aqueous solution of sodium hydrogencarbonate (5mL). The aqueous layer was extracted with dichloromethane. The organic layers were dried over magnesium sulfate, the solvent removed under reduced pressure to afford a crude product, which was purified by reversed phase chromatography to yield 8 mg of the title compound. ^{1}H NMR ($CDCl_3$): δ 8.53 (s, 1H), 8.31 (d, J = 5.1 Hz, 1H), 8.28 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 7.42-7.34 (m, 4H), 7.21 (dd, J = 1.5/5.2 Hz, 1H), 7.10 (m, 2H), 7.01 (dd, J = 1.3/5.2 Hz, 1H), 6.84 (s, 1H), 3.49 (m, 1H), 3.33 (s, 3H), 2.37 (1H), 2.05-1.89 (m, 4H), 1.80-1.76 (m, 2H), 1.55-1.47 (m, 2H).

MS (TSP) *m/z* 403 (M+1).

Example 15

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*trans*-4-methoxy-cyclohexanecarboxamide

Oxalyl chloride (171 mg, 1.35 mmol) was slowly added to a solution of 4-methoxy-cylohexanecarboxylic acid (70 mg, 0.45 mmol) in 2 mL of dichloromethane under nitrogen at 20 °C. After 30 min of stirring, the mixture was concentrated under vacuum to afford a colorless oil which was diluted in 1.0 mL of dichloromethane. This solution was then added to a solution of *N*-(2-fluorophenyl-4,4'-bipyridine-2,2'-diamine (127 mg, 0.45 mmol) in 5 mL of pyridine. After 5 min of stirring, 5 mL of a saturated aqueous solution of sodium hydrogencarbonate was added and the aqueous layer extracted with dichloromethane. The organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure to afford a crude product, which was purified by reversed phase chromatography to yield 10 mg of the title compound. ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 8.32 (d, J = 5.3 Hz, 1H), 8.27(d, J = 5.2 Hz, 1H), 8.17 (s, 1H), 7.40-7.36 (m, 2H), 7.21 (dd, J = 1.5/5.2 Hz, 1H), 7.08 (m, 2H), 7.00 (dd, J = 1.4/5.3 Hz, 1H), 6.94 (s, 1H), 6.66 (s, 1H), 3.39 (s, 3H), 3.20 (m, 1H), 2.30-2.06 (m, 5H), 1.64 (m, 2H), 1.30 (m, 2H). ^{19}F NMR ($CDCl_3$): δ -119.48 (m, 1F).

MS (ES) *m/z* 421 (M+1).

Example 16

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*cis*-4-methoxy-cyclohexanecarboxamide

Oxalyl chloride (171 mg, 1.35 mmol) was slowly added to a solution of 4-methoxy-cylohexanecarboxylic acid (70 mg, 0.45 mmol) in 2 mL of dichloromethane under nitrogen at 20 °C. After 30 min of stirring, the mixture was concentrated under vacuum to afford a colorless oil which was diluted in 1.0 mL of dichloromethane. This solution was then added to a solution of *N*-(2-fluorophenyl-4,4'-bipyridine-2,2'-diamine (127 mg, 0.45 mmol) in 5 mL of pyridine. After 5 min of stirring, 5 mL of a saturated aqueous solution of sodium hydrogencarbonate was added and the aqueous layer extracted with dichloromethane. The organic layers were dried with magnesium sulfate, filtered and concentrated under reduced

pressure to afford a crude product, which was purified by reversed phase chromatography to yield 17 mg of the title compound. ^{1}H NMR (CDCl$_3$): δ 8.52 (d, J = 0.8 Hz, 1H), 8.31 (d, J = 5.2 Hz, 1H), 8.27 (s, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.40-7.37 (m, 2H), 7.19 (dd, J = 1.6/5.2 Hz, 1H), 7.08 (m, 2H), 6.98 (dd, J = 1.5/5.3 Hz, 1H), 6.95 (s, 1H), 6.85 (s, 1H), 3.48 (m, 1H), 3.33 (s, 3H), 2.38 (m, 1H), 2.05-1.93 (m, 4H), 1.77 (m, 2H), 1.51 (m, 2H). ^{19}F NMR (CDCl$_3$): δ -119.91 (m, 1F).
MS (ES) *m/z* 421 (M+1).

Example 17

N-(6-methylpyridin-2-yl)-*N*'-phenyl-4,4'-bipyridine-2,2'-diamine

To a mixture of (N-phenyl-4,4'-bipyridine-2,2'-diamine (53 mg, 0.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol), 1.1'-bis(diphenylphosphino)ferrocene (11 mg, 0.02 mmol) and sodium *tert*-butoxide (14.4 mg, 0.15 mmol) in 2 ml dry dioxane under nitrogen was added 2-bromo-6-methylpyridine (34.5 mg, 0.20 mmol). The mixure was stirred under argon for 14 h at 100 °C, filtered, evaporated under reduced pressure, and chromatographed on silica in isooctane:ethyl acetate 1:1. Appropriate fractions were combined and concentrated to dryness to yield 40 mg (56 %) of the title compound as a pale syrup. ^{1}H NMR (CDCl$_3$) δ 8.27 (d, J=5.4 Hz, 2H), 7.98 (s, 1H, NH), 7.87 (s, 1H), 7.47 (t, J=7.7 Hz, 1H), 7.34 (s, 2H), 7.33 (d, J=1.5 Hz, 2H), 7.31 (s, 1H, NH), 7.28 (d, 8.2 Hz, 1H), 7.10 (s, 1H), 7.06 (m, 1H), 6.95 (ddd, J=1.6/ 5.3/ 9.65, 2H), 6.70 (d, 7.5 Hz, 1H), 2.40 (s, 3H).
HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 354 (M+1). C22H19N5, MW=353.4.

Example 18

N-phenyl-*N*'-pyridin-2-yl-4,4'-bipyridine-2,2'-diamine

To a mixture of (N-phenyl-4,4'-bipyridine-2,2'-diamine (27 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol), 1.1'-bis(diphenylphosphino)ferrocene (11 mg, 0.02 mmol) and sodium tert-butoxide (14.4 mg, 0.15 mmol) in 2 ml dry dioxane under nitrogen was added 2-bromopyridine (15.8 mg, 0.10 mmol). The mixure was stirred under argon for 14 h at 95 °C, filtered, evaporated under reduced pressure, and chromatographed on C8-silica using an automated preparative HPLC system (Waters 2767/2525) with a gradient of 35% - 100% acetonitrile in 0.05M aqueous ammonium acetate. Appropriate fractions were combined and concentrated to dryness to yield 2 mg (6 %) of the title compound

HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 340 (M+1). C21H17N5, MW=339.4

Example 19

_N_-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-_N'_-phenyl-4,4'-bipyridine-2,2'-diamine

To a mixture of (N-phenyl-4,4'-bipyridine-2,2'-diamine (27 mg, 0.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (9.2 mg, 0.01 mmol), 1.1'-bis(diphenylphosphino)ferrocene (11 mg, 0.02 mmol) and sodium *tert*-butoxide (14.4 mg, 0.15 mmol) in 2 ml dry dioxane under nitrogen was added 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (32 mg, 0.10 mmol). The mixure was stirred under argon for 16 h at 95 °C, filtered, evaporated under reduced pressure, and chromatographed on C8-silica (Waters XTerra MS C8, 19x300mm, 7um) using an automated preparative HPLC system (Gilson autopreparative HPLC, diode array detection) with a gradient of 20% - 60% acetonitrile in 0.1 M aqueous ammonium acetate for 13 minutes at 20ml/min. Appropriate fractions were combined and concentrated to dryness to yield 26.6 mg (53 %) of the title compound. The material was dissolved in methanol and 1M hydrochloric acid (0.5 mL) was added. The solution was evaporated to dryness, dissolved in water and freeze dried. ^{1}H NMR (D_2O) δ 7.86 – 6.80 (15H), 3.65 (d, J = 12.0 Hz, 2H), 3.38 (d, 2H), 3.02 (m, 2H), 2.69 (s, 3H), 2.59 (m, 2H).

HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with m/z 501 (M+1). C27H28N6O2S, MW=500.6.

Examples 20-27

Compounds 20-27 were prepared according to the procedure set forth in Example 19, using the appropriate bromoaryl or bromoheteroaryl derivative and *N*-phenyl-4,4'-bipyridine-2,2'-diamine prepared as described in example 11.

Example	Name	MW	Found m/z	Yield
20	N-phenyl-N'-pyridin-3-yl-4,4'-bipyridine-2,2'-diamine	339.4	340	9.3 mg
21	N-phenyl-N'-pyrimidin-2-yl-4,4'-bipyridine-2,2'-diamine	340.4	341	14.0 mg
22	N-phenyl-N'-pyrimidin-5-yl-4,4'-bipyridine-2,2'-diamine	340.4	341	6.1 mg
23	(2E)-1-{4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]phenyl}-3-(dimethylamino)prop-2-en-1-one	435.5	436	10.8 mg
24	4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-pyrrolidin-1-ylethyl)benzenesulfonamide	514.7	515	31.1 mg
25	4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-morpholin-4-ylethyl)benzenesulfonamide	530.7	531	15.3 mg
26	N-{4-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl}-N'-phenyl-4,4'-bipyridine-2,2'-diamine	514.7	515	17.8 mg
27	N-phenyl-N'-pyridin-4-yl-4,4'-bipyridine-2,2'-diamine	339.4	340	4.0 mg

Example 28

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide

Tetrahydrofuran-3-carboxylic acid (11.6 mg, 0.1 mmol) was dissolved in dichloromethane (0.5 ml) under nitrogen. Dimethylformamide (50 uL) is added. Oxalyl chloride (43 uL, 0.5 mmol) was dissolved in dichloromethane (0.5 ml) and added dropwise to the carboxylic acid. After 10 minutes of stirring the solution was evaporated to dryness, dissolved in dichloromethane (1 ml), and evaporated again to dryness. Pyridine (2 mL) was added, followed by *N*-phenyl-4,4'-bipyridine-2,2'-diamine (26 mg, 0.1 mmol) in dry tetrahydrofurane (0.5 mL). The mixture was stirred 16 h at room temperature. HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 361 (M+1). C21H20N4O2, MW=360.4. ^{1}H NMR (CD_3OD): δ 10.51 (s, 1H), 8.86 (s, 1H), 8.40 (s, 1H), 8.31 (d, J = 5.2 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.45-7.00 (m, 8H), 4.01-3.90 (m, 3H), 3.77 (m, 1H), 3.15 (m, 1H), 2.20 (m, 2H).

Example 29

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-piperidin-1-ylpropanamide

3-Piperidin-1-ylpropanoic acid (15.7 mg, 0.1 mmol) is weighed into a 5 ml glass tube. Dichloromethane (1 mL) is added followed by dimethylformamide:dichloromethane (1:10, 50 uL). Oxalyl chloride (43 uL, 0.5 mmol) diluted with dichloromethane (60 uL) is added. The mixture is agitated at room temperature under argon for 2 hours, or until bubbling has ceased and a homogenous solution is obtained. Then 250 uL of this solution (corresponding to 0.02 mmol carboxylic acid) is transferred to a 1 mL polystyrene tube in a 96-well format box and evaporated to dryness under a stream of heated nitrogen (3 minutes, 35°C). The remaining syrup is dissolved in dichloromethane (100 uL), and *N*-phenyl-4,4'-bipyridine-2,2'-diamine (5.2 mg, 0.02 mmol) in pyridine (300 uL) is added. The well is capped and agitated on an orbital shaker for 16 hours at room temperature under nitrogen. The solution is evaporated to dryness under a stream of heated nitrogen (5 minutes, 50°C), The crude material is dissolved in methanol, filtered and chromatographed on C8-silica using an automated preparative HPLC system (Waters 2767/2525) with a gradient of 35%-100% acetonitrile in 0.05M aqueous ammonium acetate. Appropriate fractions were combined and concentrated to dryness to yield 3.9 mg (49 %) of the title compound. HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 402 (M+1). $C_{24}H_{27}N_5O$, MW=401.5.

Compounds 30-73 were prepared according to the procedure set forth in Example 29, using the appropriate carboxylic acid and *N*-phenyl-4,4'-bipyridine-2,2'-diamine prepared as described in example 11.

Example 30-73

Example	Name	MW	Found m/z	Yield (mg)
30	N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide	360.4	361	3.1
31	N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide	367.4	368	3.5
32	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide	409.5	410	0.8
33	N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide	427.5	428	0.1
34	N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide	405.5	406	0.1
35	N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide	367.4	368	2.7
36	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide	356.4	357	0.1
37	N-(2'-anilino-4,4'-bipyridin-2-yl)-1,2,3-thiadiazole-4-carboxamide	374.4	375	0.5
38	N-(2'-anilino-4,4'-bipyridin-2-yl)isoxazole-5-carboxamide	357.4	358	2.6
39	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-3-carboxamide	371.4	372	5.3
40	N-(2'-anilino-4,4'-bipyridin-2-yl)pyrazine-2-carboxamide	368.4	369	2.7
41	N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-imidazole-4-carboxamide	370.4	371	4.9

42	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-furamide	356.4	357	0.5
43	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxybenzamide	396.4	397	2.4
44	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-bromo-2-furamide	435.3	435	4.2
45	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-(methylthio)nicotinamide	413.5	414	1.3
46	methyl 4-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}benzoate	424.5	425	0.8
47	3-(acetylamino)-N-(2'-anilino-4,4'-bipyridin-2-yl)benzamide	423.5	424	0.3
48	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide	424.5	425	3.6
49	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-[(pyridin-2-ylthio)methyl]-2-furamide	479.6	480	0.8
50	N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide 1-oxide	383.4	384	0.5
51	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-hydroxypyridine-2-carboxamide	383.4	384	0.3
52	N-(2'-anilino-4,4'-bipyridin-2-yl)-6-bromopyridine-2-carboxamide	446.3	446	6.2
53	N-(2'-anilino-4,4'-bipyridin-2-yl)isonicotinamide 1-oxide	383.4	384	2.3

54	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-hydroxynicotinamide	383.4	384	0.4
55	N-(2'-anilino-4,4'-bipyridin-2-yl)-6-hydroxypyridine-2-carboxamide	383.4	384	2.6
56	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-benzoylpyridine-2-carboxamide	471.5	472	1.8
57	N-(2'-anilino-4,4'-bipyridin-2-yl)-6-methylpyridine-2-carboxamide	381.4	382	0.8
58	N-(2'-anilino-4,4'-bipyridin-2-yl)-3,5-dimethylisoxazole-4-carboxamide	385.4	386	0.5
59	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-methoxynicotinamide	397.4	398	0.6
60	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methyl-1,2,3-thiadiazole-5-carboxamide	388.5	389	5.6
61	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloroisonicotinamide	401.9	402	5.7
62	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-4-carboxamide	371.4	372	1.3
63	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methylisoxazole-4-carboxamide	371.4	372	4.3
64	N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-pyrrole-2-carboxamide	369.4	370	2.1
65	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloronicotinamide	401.9	402	4.1

66	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-chloro-1H-indole-2-carboxamide	439.9	440	0.4
67	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-chloro-1H-pyrazole-3-carboxamide	390.8	391	0.9
68	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methyl-1H-pyrazole-3-carboxamide	370.4	371	0.6
69	(2E)-N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(3-furyl)acrylamide	382.4	383	0.7
70	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanamide	451.5	452	0.7
71	N'-(2'-anilino-4,4'-bipyridin-2-yl)-N,N-dimethylsuccinamide	389.5	390	0.3
72	N-(2'-anilino-4,4'-bipyridin-2-yl)-2-[(4-chlorophenyl)sulfonyl]acetamide	479.0	479	1.1
73	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide	373.4	374	1.3

Example 74

***N*-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide**

General procedure:

To a mixture of 3-Methoxypropanoic acid (11 mg, 0.1 mmol), *N*-phenyl-4,4'-bipyridine-2,2'-diamine (26 mg, 0.1 mmol), hydroxybenzotriazole (14 mg, 0.1 mmol), polystyrene bound diisopropylamine (N,N-(Diisopropyl)aminomethylpolystyrene, 32 mg, 0.12 mmol) and polystyrene bound carbodiimide (N-cyclohexylcarbodiimide-N'-propyloxymethyl polystyrene, 158 mg, 0.3 mmol) was added 2 mL dimethylformamide 1. The mixture was stirred at 120°C for 48h under argon. Filtering and evaporation gave a brown syrup which was dissolved in dimethylsulfoxide (200 uL) and subjected to chromatography on C8-silica using an automated preparative HPLC system (Waters 2767/2525) with a gradient of 25% - 45% acetonitrile in 0.05M aqueous ammonium acetate. Appropriate fractions were combined and concentrated to dryness under vacuum to yield 5.3 mg of the title compound. HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 349 (M+1). C20H20N4O2, MW=348.4.

Examples 75-85

Compounds 75-85 were prepared according to the procedure set forth in Example 74, using the appropriate carboxylic acid and *N*-phenyl-4,4'-bipyridine-2,2'-diamine prepared as described in example 11.

Example	Name	MW	Found m/z	Yield
75	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxycyclohexanecarboxamide	402.5	403	9.2 mg
76	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide	348.4	349	5.3 mg
77	N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide	360.4	361	17.4 mg
78	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)butanamide	375.5	376	9.6 mg
79	N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide	367.4	368	9.2 mg
80	N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide	409.5	410	3.8 mg
81	N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide	427.5	428	3.3 mg
82	N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide	405.5	406	3.1 mg
83	N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylpyrazine-2-carboxamide	382.4	383	3.9 mg

84	N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide	367.4	368	9.2 mg
85	N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide	356.4	357	5.5 mg

Example 86

N-(2'-anilino-4,4'-bipyridin-2-yl)-*N*'-phenylurea

Procedure A:

To a solution of and *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.5 mmol) in dioxane (5 mL) under nitrogen was added phenyl isocyanate (60 mg, 0.5 mmol) dissolved in dioxane (1 mL). The mixture was stirred at room temperature for 16 hours. Precipitated material was filtered off and verified by NMR and HPLC-MS to be the title compound (104 mg, 55%) in 96% purity (uv-detection).. ^{1}H NMR (DMSO-D_6) δ 8.40 (d, J=5.6 Hz, 1H), δ 8.30 (d, J=5.6 Hz, 1H), 7.99(d, J=5.1 Hz, 1H), 7.73 (d, J=8.1 Hz, 2H), 7.54 (d, J=8.1 Hz, 2H), 7.30 (m, 5H), 7.15 (s, 1H, NH), 7.04 (m, 2H), 6.92 (t, 7.1 Hz, 1H). ^{13}C NMR (DMSO-D6) δ 156.7, 152.1, 148.5, 147.5, 145.9, 141.5, 139.0, 138.9, 128.9, 128.7, 122.6, 120.7, 118.8, 118.7, 118.1, 115.3, 111.8, 108.8, 107.9. ^{15}N NMR (DMSO-D_6) δ -275.0, -260.4, -269.5, -113.3, 108.1. The chemical shifts and positions of the nitrogen atoms were determined using ^{15}N HSQC and ^{15}N HMBC in combination with ^{1}H-1H COSY. ^{15}N chemical shifts are given relative external nitro methane at 0.0 ppm. The ^{15}N experiments were performed on a Bruker DRX600 NMR Spectrometer, operating at 600 MHz for proton 60 MHz for nitrogen-15 and equipped with a 5mm TXI probe with Z-gradients. The experiments were performed at 22 degrees Centigrade.

HPLC-MS (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid. UV-diode array detector, CLND and MSD-ESI detection) shows a single compound with *m/z* 382 (M+1). C24H27N5O, MW=381.4.

Procedure B:

To a solution of phenyl isocyanate (72 uL, 0.5 M in dioxane, 0.036 mmol) in a 2 mL deep-well 96-well plate was added *N*-phenyl-4,4'-bipyridine-2,2'-diamine (7.9 mg, 0.03 mmol) in dioxane (200 uL) under nitrogen. The plate was agitated on an orbital shaker at room temperature for 16 hours. Precipitated material was filtered off and dissolved in dimethylsulfoxide. Analysis and quantification of the product was done using an Agilent HP1100 HPLC-MS system (Waters Exterra C8-column, 8.6 min gradient of 0-100% methanol containing 0.1% trifluoroacetic acid) equipped with UV-diode array detector, CLND (nitrogen detector) and MSD-ESI detector.

Compounds 87-166 were prepared according to the procedure set forth in Procedure B, using the appropriate isocyanate derivative and *N*-phenyl-4,4'-bipyridine-2,2'-diamine prepared as described in example 11.

Example 87-166

Entry	Name	MW	Found m/z	Yield (mg)
87	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-phenylurea	381.4	382	3.6
88	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[1-(4-bromophenyl)ethyl]urea	488.4	488	0.1
89	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-thien-3-ylurea	387.5	388	2.8
90	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylphenyl)urea	395.5	396	1.9
91	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylphenyl)urea	395.5	396	1.8
92	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorophenyl)urea	399.4	400	2.9
93	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorophenyl)urea	399.4	400	0.4
94	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-fluorophenyl)urea	399.4	400	0.1

95	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(chloromethyl)phenyl]urea	429.9	430	2.2
96	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-cyanophenyl)urea	406.4	407	1.7
97	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-cyanophenyl)urea	406.4	407	0.3
98	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-cyanophenyl)urea	406.4	407	0.1
99	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dimethylphenyl)urea	409.5	410	0.8
100	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dimethylphenyl)urea	409.5	410	0.3
101	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethylphenyl)urea	409.5	410	0.7
102	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-ethylphenyl)urea	409.5	410	1.6
103	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxyphenyl)urea	411.5	412	2.6
104	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-methoxyphenyl)urea	411.5	412	0.2
105	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxyphenyl)urea	411.5	412	0.2
106	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-fluoro-2-methylphenyl)urea	413.5	414	0.4
107	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorobenzyl)urea	413.5	414	2.7
108	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluoro-5-methylphenyl)urea	413.5	414	0.3
109	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorobenzyl)urea	413.5	414	1.5
110	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorophenyl)urea	415.9	416	0.3

111	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chlorophenyl)urea	415.9	416	0.2
112	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea	429.9	430	2.3
113	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-difluorophenyl)urea	417.4	418	0.2
114	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-difluorophenyl)urea	417.4	418	0.1
115	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorobenzyl)urea	464.4	464	1.6
116	N-(4-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea	423.5	424	0.2
117	N-(3-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea	423.5	424	3.2
118	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-isopropylphenyl)urea	423.5	424	0.4
119	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropylphenyl)urea	423.5	424	0.9
120	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-ethyl-6-methylphenyl)urea	423.5	424	0.2
121	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-mesitylurea	423.5	424	0.1
122	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-propylphenyl)urea	423.5	424	1.0
123	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(dimethylamino)phenyl]urea	424.5	425	0.1
124	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-1,3-benzodioxol-5-ylurea	425.4	426	0.2
125	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxy-2-methylphenyl)urea	425.5	426	0.4
126	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxy-5-methylphenyl)urea	425.5	426	0.1

127	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethoxyphenyl)urea	425.5	426	0.9
128	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxybenzyl)urea	425.5	426	1.6
129	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-nitrophenyl)urea	426.4	427	0.5
130	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-nitrophenyl)urea	426.4	427	0.6
131	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(methylthio)phenyl]urea	427.5	428	3.3
132	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(methylthio)phenyl]urea	427.5	428	0.4
133	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylbenzyl)urea	409.5	410	2.7
134	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2-methylphenyl)urea	429.9	430	0.3
135	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chloro-5-methylphenyl)urea	429.9	430	0.4
136	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea	429.9	430	2.1
137	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-fluorophenyl)urea	433.9	434	0.2
138	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3,4-trifluorophenyl)urea	435.4	436	0.1
139	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butylphenyl)urea	437.5	438	0.1
140	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropyl-6-methylphenyl)urea	437.5	438	0.1
141	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-tert-butylphenyl)urea	437.5	438	0.4
142	methyl 4-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)benzoate	439.5	440	0.1

143	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dimethoxyphenyl)urea	441.5	442	3.6
144	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dimethoxyphenyl)urea	441.5	442	0.8
145	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-methoxyphenyl)urea	445.9	446	0.8
146	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(difluoromethoxy)phenyl]urea	447.4	448	0.6
147	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[2-(trifluoromethyl)phenyl]urea	449.4	450	0.2
148	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(trifluoromethyl)phenyl]urea	449.4	450	0.1
149	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(trifluoromethyl)phenyl]urea	449.4	450	0.1
150	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dichlorophenyl)urea	450.3	450	0.1
151	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dichlorophenyl)urea	450.3	450	0.0
152	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorophenyl)urea	450.3	450	0.3
153	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dichlorophenyl)urea	450.3	450	0.2
154	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-dichlorophenyl)urea	450.3	450	1.2
155	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-bromo-3-methylphenyl)urea	474.4	474	0.1
156	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-dichloropyridin-4-yl)urea	451.3	451	0.1
157	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butyl-2-methylphenyl)urea	451.6	452	0.0
158	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[5-methyl-2-(trifluoromethyl)-3-furyl]urea	453.4	454	0.2

159	ethyl 3-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)benzoate	453.5	454	0.2
160	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butoxyphenyl)urea	453.5	454	0.2
161	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(trifluoromethoxy)phenyl]urea	465.4	466	0.1
162	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-diisopropylphenyl)urea	465.6	466	0.1
163	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylbenzyl)urea	409.5	410	0.5
164	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea	475.9	476	1.6
165	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-{4-[(trifluoromethyl)thio]phenyl}urea	481.5	482	0.1
166	N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3,5-bis(trifluoromethyl)phenyl]urea	517.4	518	0.1

Example 167

1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide

Procedure as example 14. Reaction with 1-acetylpiperidine-4-carboxylic acid for 5 days. Purification on silica gel (0 to 10% MeOH in CH_2Cl_2) gave 5 mg (5%) of the title compound. The product was treated with 1 eq. trifluoroacetic acid and freeze dried to give the TFA salt.

MS (ES) *m/z* 416 (M+1).

Example 168

***N*-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide**

Procedure as example 14. Reaction with D,L-pyroglutamic acid for 5 days gave 12 mg (13%) of the title compound. The product was treated with 1 eq. TFA and freeze dried to

give the trifluoroacetic acid salt. ^{1}H NMR (CD_3OD): δ 8.54 - 8.48 (m, 2H), 7.98 (d, J = 6.5 Hz, 1H), 7.56 –7.35 (m, 7H), 7.30 (dd, J = 6.5, 2 Hz, 1H), 4.44 (m, 1H), 2.65 – 2.15 (m, 4H), 1.30 (m, 1H).
MS (ES) *m/z* 374 (M+1).

Example 169

N^3-acetyl-*N*^{1}-(2'-anilino-4,4'-bipyridin-2-yl)-β-alaninamide

Procedure as example 14. Reaction with *N*-acetyl-β-alanine for 5 days gave 30 mg (31%) of the title compound. The product was treated with 1 eq. TFA and freeze dried to give the trifluoroacetic acid salt. ^{1}H NMR (CD_3OD): δ 8.50 - 8.46 (m, 2H), 7.96 (d, J = 6.5 Hz, 1H), 7.59 –7.39 (m, 7H), 7.33 (dd, J = 6.5, 1.5 Hz, 1H), 3.53 (m, 2H), 2.68 (m, 2H), 1.92 (s, 3H).

Example 170

N-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide

Procedure as example 14. Reaction with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid for 8 days. Reverse phase chromatography was followed by boc removal with TFA/ CH_2Cl_2 1:1. A second reverse phase chromatography gave 16 mg (17%) of the title compound as the free base. ^{1}H NMR (CD_3OD): δ 8.42 (s, 1H), 8.37 (d, J = 5 Hz, 1H), 8.19 (d, J = 5.5 Hz, 1H), 7.54 (m, 2H), 7.37 (dd, J = 5.5, 1.5 Hz, 1H), 7.29 (m, 2H), 7.10 (s, 1H), 7.03 (dd, J = 5.5, 1.5 Hz, 1H), 6.97 (m, 1H), 3.11 (m, 2H), 2.64 (m, 3H), 1.87 (m, 2H), 1.73 (m, 2H).

Example 171

3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)butanamide

Procedure as example 14. Reaction with (+/-)-3-[(*tert*-butoxycarbonyl)amino]butanoic acid for 5 days followed by N-boc removal as for 26757 gave 10 mg (11%) of title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.43 (s, 1H), 8.36 (d, J = 5 Hz, 1H), 8.19 (d, J = 5 Hz, 1H), 7.53 (m, 2H), 7.36 (dd, J = 5, 2 Hz, 1H), 7.28 (m, 2H), 7.09 (s, 1H), 7.02 (dd, J = 5.5, 1.5 Hz, 1H), 6.97 (m, 1H), 3.40 (m, 1H), 3.34 (s, 3H), 2.60-2.43 (m, 2H), 1.18 (d, J = 6.5 Hz, 3H).
MS (ES) *m/z* 348 (M+1).

Example 172

N-(2'-anilino-4,4'-bipyridin-2-yl)-L-prolinamide

Procedure as example 14. Reaction with 1-(*tert*-butoxycarbonyl)-L-proline for 8 days followed by N-boc removal as for 26757 gave 7 mg (9%) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.48 (s, 1H), 8.37 (d, J = 5 Hz, 1H), 8.20 (d, J = 5.5 Hz, 1H), 7.53 (m, 2H), 7.40 (dd, J = 5, 1.5 Hz, 1H), 7.29 (m, 2H), 7.10 (s, 1H), 7.03 (dd, J = 5, 1.5 Hz, 1H), 6.97 (m, 1H), 3.86 (m, 1H), 3.03 (m, 2H), 2.23 (m, 1H), 1.93 (m, 1H), 1.79 (m, 2H).

MS (ES) *m/z* 360 (M+1).

Example 173

N-(2'-anilino-4,4'-bipyridin-2-yl)acetamide

N-phenyl-4,4'-bipyridine-2,2'-diamine (50 mg, 0.19 mmol) was dissolved in pyridine (2 mL) and acetyl chloride (14 µL, 0.20 mmol) was added at 0°C and stirred 1h at 25°C followed by concentration *in vacuo*. Purification by reverse phase chromatography gave 16 mg (27%) of the title compound as the free base. ^{1}H NMR (CD_3OD): δ 8.50 (m, 1H), 8.16 (s, 1H), 8.01 (d, J = 5 Hz, 1H), 7.68 (m, 1H), 7.59 (m, 2H), 7.52-7.44 (m, 4H), 7.36 (m, 1H), 3.22 (s, 3H).

MS (ES) *m/z* 305 (M+1).

Example 174

Methyl 2'-anilino-4,4'-bipyridin-2-ylcarbamate

Procedure as example 173. Methyl chloroformate (16 µL, 0.20 mmol) was added at 0°C followed by a second portion (5 mL) after 12 h and stirring was continued for 2 d at 25°C. Purification by silica gel chromatography (0 to 10% MeOH in EtOAc) gave 5 mg (8%) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.45 (m, 1H), 8.13 (s, 1H), 7.97 (d, J = 6.5 Hz, 1H), 7.58 (m, 2H), 7.51 (m, 1H), 7.48-7.43(m, 4H), 7.35 (m, 1H), 3.84 (s, 3H).

MS (ES) *m/z* 322 (M+1).

Example 175

N-(2'-anilino-4,4'-bipyridin-2-yl)methanesulfonamide

Procedure as example 173. Methanesulfonylchloride (16 µL, 0.20 mmol) was added at 0°C and stirring was continued for 3 d at 25°C. Purification by silica gel chromatography (0 to 5% MeOH in EtOAc) was followed by reverse phase chromatography to give 2 mg (3%) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.46 (m, 1H), 7.96 (d, J = 6.5 Hz, 1H), 7.56 (m, 2H), 7.47-7.28 (m, 7H, 3.29 (s, 3H).
MS (ES) *m/z* 341 (M+1).

Example 176

N-(2'-anilino-4,4'-bipyridin-2-yl)cyclohexanecarboxamide

Procedure as example 173. Cyclohexanecarbonyl chloride (28 µL, 0.20 mmol) was added at 0°C and stirring was continued for 12 h at 25°C. Purification by reverse phase chromatography gave 4 mg (5%) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.46 (m, 2H), 8.00 (d, J = 6.5 Hz, 1H), 7.55-7.40 (m, 5H), 7.35 (m, 2H), 7.27 (m, 1H), 2.50 (m, 1H), 1.97-1.22 (m, 10H).
MS (ES) *m/z* 373 (M+1).

Example 177

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-2-carboxamide

Procedure as example 14. Reaction with 1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (described in Costa, Brian R. de; Dominguez, Celia; He, Xiao-shu; Williams, Wanda; Radesca, Lilian; Bowen, Wayne; J.Med.Chem; 35; 23; 1992; 4334-4343.) for 7 days was followed by workup and treatment with TFA/ CH_2Cl_2 , 1:1 for 30 min. Purification with reverse phase chromatography gave 5 mg (13 µmol) of the N-boc deprotected product which was dissolved in CH_2Cl_2 (2 mL) together with triethylamine (2.1 µL, 15 µmol) and treated with acetic anhydride (1.4 µL, 14 µmol). After stirring 12 h at 25°C and evaporation of the solvent *in vacuo*, purification with reverse phase chromatography gave 2 mg (1%, 3 steps) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.40 (m, 2H), 8.20 (m, 1H), 7.54 (m, 2H), 7.40

(m, 1H), 7.29 (m, 2H), 7.11 (m, 1H), 7.04 (m, 1H), 6.97 (m, 1H), 2.20 (s, 3H), 2.20-0.98 (m, 9H).

MS (ES) *m/z* 416 (M+1).

Example 178

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide

Procedure as example 14. Reaction with 1-acetylpiperidine-3-carboxylic acid (described in : Zalucky et al., J. Pharm. Sci., 1965, 54, 687-693) for 5 days. Purification with reverse phase chromatography gave 3 mg (3%) of the title compound. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. ^{1}H NMR (CD_3OD): δ 8.52-8.42 (m, 2H), 7.95 (d, J = 6.5 Hz, 1H), 7.58 (m, 3H), 7.51-7.42 (m, 4H), 7.34 (dd, J = 7, 2 Hz, 1H), 4.53 (m, 1H), 4.19 (m, 1H), 3.98-3.84 (m, 2H), 2.99 (m, 1H), 2.13 (s, 3H), 2.13-1.26 (m, 4H).

MS (ES) *m/z* 416 (M+1).

Example 179

Ethyl 4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-4-oxobutanoate

4-Ethoxy-4-oxobutanoic acid (36 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (142 mg, 0.375 mmol) were diluted in 4 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (64 mg, 87μL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (65 mg, 0.25 mmol) in dry *N, N*-dimethylformamide (1mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 25 % (25 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.04 (s, 1 H), 8.45 (s, 1 H), 8.30 (d, *J*=6.1 Hz, 1 H), 8.25 (d, *J*=4.5 Hz, 1 H), 7.43 - 7.32 (m, 5 H), 7.20 - 7.14 (m, 1 H), 7.09 - 7.05 (m, 2 H), 6.96 (d, *J*=5.6 Hz, 1 H), 4.16 (q, *J*=7.1 Hz, 2 H), 2.76 - 2.66 (m, 4 H), 1.27 - 1.22 (t, *J*=7.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 172.64 (s, 1 C), 170.50 (s, 1 C), 156.58 (s, 1 C), 152.20 (s, 1 C), 148.38 (s, 1 C), 148.08 (s, 1 C), 147.85 (s, 1 C), 139.97 (s, 1 C), 129.40 (s, 4 C), 123.30 (s, 1 C), 120.66 (s, 1 C), 117.56 (s, 1 C), 113.07 (s, 1 C), 111.89 (s, 1 C), 106.39 (s, 1 C), 60.87 (s, 1 C), 31.97 (s, 1 C), 29.03 (s, 1 C), 14.15 (s, 1 C).

MS (TSP) *m/z* (M+1) : 343, 391.

Example 180

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-2-carboxamide (*E1*) and (*E2*)

Tetrahydrofuran-2-carboxylic acid (58 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (285 mg, 0.75 mmol) were diluted in 6 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (129 mg, 174 µL, 1.0 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.50 mmol) in dry *N, N*-dimethylformamide (2 mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 44 % (81 mg) of the racemate. Both enantiomers were separated on a chiral column to afford : 25 mg of *E1* and 22 mg of *E2*. ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.12 (s, 1 H), 8.51 (s, 1 H), 8.36 (d, *J*=4.5 Hz, 1 H), 8.30 (d, *J*=6.1 Hz, 1 H), 7.42 - 7.34 (m, 4 H), 7.23 (d, *J*=3.5 Hz, 1 H), 7.11 - 7.04 (m, 2 H), 7.01 (d, *J*=5.1 Hz, 1 H), 6.64 (s, 1 H), 4.50 (dd, *J*=8.6, 5.6 Hz, 1 H), 4.12 - 4.03 (m, 1 H), 4.02 - 3.92 (m, 1 H), 2.44 - 2.33 (m, 1 H), 2.19 (td, *J*=13.4, 6.1 Hz, 1 H), 2.02 - 1.90 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 172.32 (s, 1 C), 156.63 (s, 1 C), 151.55 (s, 1 C), 149.15 (s, 1 C), 148.74 (s, 1 C), 148.62 (s, 1 C), 140.15 (s, 1 C), 129.38 (s, 2 C), 123.10 (s, 1 C), 120.38 (s, 2 C), 117.92 (s, 1 C), 113.29 (s, 1 C), 111.51 (s, 1 C), 106.26 (s, 1 C), 78.52 (s, 1 C), 69.76 (s, 1 C), 31.87 (s, 1 C), 25.58 (s, 1 C).

MS (TSP) *m/z* (M+1): 361.

Example 181

(*S*)-3 *N*^{2}-acetyl-*N*^{1}-(2'-anilino-4,4'-bipyridin-2-yl)methioninamide

(S)-*N*-acetyl-L-methionine (96 mg, 0.50 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (285 mg, 0.75 mmol) were diluted in 6 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (129 mg, 174 µL, 1.0 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.50 mmol) in dry *N, N*-dimethylformamide (2 mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 25 % (54 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.27 (s, 1 H), 8.42 (s, 1 H), 8.33 (d, *J*=5.1 Hz, 1 H), 8.26 (d, *J*=5.6 Hz, 1 H), 7.42 - 7.33 (m, 4 H), 7.22 (d, *J*=5.6 Hz, 1 H), 7.11 - 7.05 (m, 3 H), 6.97 (d, *J*=5.6 Hz, 1 H), 6.44 (d, *J*=8.1 Hz, 1 H), 4.85 - 4.77 (m, 1 H), 2.67 - 2.56 (m, 2 H), 2.27 - 2.18 (m, 1 H), 2.13 (s, 3 H), 2.09 - 2.00 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 170.50 (s, 1 C), 170.20 (s, 1 C), 156.69 (s, 1 C), 151.73 (s, 1 C), 148.96 (s, 1 C), 148.89 (s, 1 C), 148.36 (s, 1 C), 147.51 (s, 1 C), 140.08 (s, 1 C), 129.40 (s, 2 C), 123.17 (s, 1 C), 120.44 (s, 2 C), 118.07 (s, 1 C), 113.11 (s, 1 C), 111.95 (s, 1 C), 106.22 (s, 1 C), 53.35 (s, 1 C), 31.20 (s, 1 C), 30.29 (s, 1 C), 23.22 (s, 1 C), 15.38 (s, 1 C).

MS (TSP) *m/z* (M+1) : 436.

<u>Example 182</u>

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide

Tetrahydro-2*H*-pyran-4-carboxylic acid (83 mg, 0.64 mmol) was dissolved in 4 mL of thionyl chloride and the solution was stirred for 30 min at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 1 mL dichloromethane. This solution was added dropwise to a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (160 mg, 0.61 mmol) in 10 mL of pyridine. After 1h stirring, the solvent was removed under vacuum and the crude product was purified by HPLC : column : XTerra® prep MSC_8, gradient 20-80%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 48% (110 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.49 (s, 1 H), 8.32 (d, *J*=6.1 Hz, 1 H), 8.28 (d, *J*=4.5 Hz, 1 H), 8.05 (s, 1 H), 7.42 - 7.33 (m, 4 H), 7.23 -

7.19 (m, 1 H), 7.09 - 7.03 (m, 2 H), 6.99 (d, *J*=5.6 Hz, 1 H), 6.71 (s, 1 H), 4.10 - 4.02 (m, 2 H), 3.51 - 3.41 (m, 2 H), 2.59 - 2.49 (m, 1 H), 1.95 - 1.84 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 172.97 (s, 1 C), 156.66 (s, 1 C), 152.05 (s, 1 C), 149.20 (s, 1 C), 148.43 (s, 1 C), 147.38 (s, 1 C), 140.17 (s, 1 C), 129.38 (s, 2 C), 123.07 (s, 1 C), 120.35 (s, 2 C), 117.82 (s, 1 C), 113.24 (s, 1 C), 111.70 (s, 1 C), 106.29 (s, 1 C), 67.07 (s, 2 C), 43.26 (s, 1 C), 29.01 (s, 2 C).

MS (TSP) *m/z* (M+1) : 375.

Example 183

Ethyl 3-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-3-oxopropanoate

3-Ethoxy-3-oxopropanoic acid (33 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (142mg, 0.375 mmol) were diluted in 4 mL of dry *N*, *N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (64 mg, 87μL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (65 mg, 0.25 mmol) in dry *N*, *N*-dimethylformamide (1mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 27 % (25 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.59 (s, 1 H), 8.42 (s, 1 H), 8.35 (d, *J*=6.1 Hz, 1 H), 8.28 (d, *J*=6.1 Hz, 1 H), 7.41 - 7.32 (m, 4 H), 7.23 - 7.22 (m, 1 H), 7.10 - 7.04 (m, 2 H), 7.01 - 6.95 (m, 1 H), 6.81 (s, 1 H), 4.27 (q, *J*=7.1 Hz, 2 H), 3.51 (s, 2 H), 1.32 (t, *J*=7.1 Hz, 4 H).

MS (TSP) *m/z* (M+1) : 377.

Example 184

***N*-(2'-anilino-4,4'-bipyridin-2-yl)-3-(methylthio)propanamide**

3-Thiomethoxy propanoic acid (33 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (142mg, 0.375 mmol) were diluted in 4 mL of dry *N*, *N*-dimethylformamide under a nitrogen atmosphere. Diisoprylethylamine (64 mg, 87μL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (65 mg, 0.25 mmol) in dry *N, N*-dimethylformamide (1mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 27 % (25 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.67 (s, 1H), 8.47 (s, 1 H), 8.32 (d, *J*=5.1 Hz, 1 H), 8.28 (d, *J*=5.1 Hz, 1 H), 7.42 - 7.31 (m, 4 H), 7.20 (d, *J*=5.1 Hz, 1 H), 7.09 - 7.02 (m, 2 H), 6.98 (d, *J*=5.6 Hz, 1 H), 2.92 - 2.85 (m, 2 H), 2.72 (t, *J*=7.1 Hz, 2 H), 2.15 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 156.63 (s, 1 C), 149.13 (s, 1 C), 148.83 (s, 1 C), 148.39 (s, 1 C), 147.36 (s, 1 C), 147.35 (s, 1 C), 140.13 (s, 1 C), 129.34 (s, 2 C), 122.95 (s, 1 C), 120.33 (s, 1 C), 120.19 (s, 2 C), 117.78 (s, 1 C), 113.17 (s, 1 C), 111.75 (s, 1 C), 106.28 (s, 1 C), 37.35 (s, 1 C), 37.32 (s, 1 C), 29.39 (s, 1 C).

MS (TSP) *m/z* (M+1) : 365.

Example 185

(±)*N*-(2'-anilino-4,4'-bipyridin-2-yl)-2-pyrrolidin-2-ylacetamide

[1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl]acetic acid (163 mg, 0.75 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (380 mg, 1.0 mmol) were diluted in 4 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (193 mg, 258 μL, 1.5 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.50 mmol) in dry *N, N*-dimethylformamide (2 mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3x20 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 95/5). Yield : 87 % (207 mg). This compound (207 mg) was diluted in 10 mL dichloromethane under nitrogen atmosphere and the solution was cooled to 0°C. Trifluoroacetic acid (2 mL) was added dropwise and the solution stirred for 15h at 20°C. The solvents were removed under vacuum. The resulting material was diluted in MeOH

(10 mL) and mixed with Dowex. After filtration the solution was concentrated under vacuum the crude material purified by HPLC column : XTerra® prep MSC$_8$, gradient 20-80%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 38% (71 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.44 (s, 1 H), 8.34 (d, *J*=4.5 Hz, 1 H), 8.28 (d, *J*=6.1 Hz, 1 H), 7.42 - 7.33 (m, 4 H), 7.16 (d, *J*=3.5 Hz, 1 H), 7.09 - 7.02 (m, 2 H), 6.99 (d, *J*=5.1 Hz, 1 H), 6.77 (s, 1 H), 3.63 - 3.51 (m, 1 H), 3.09 - 3.02 (m, 2 H), 2.54 - 2.42 (m, 2 H), 2.05 - 1.96 (m, 1 H), 1.94 - 1.82 (m, 1 H), 1.76 (ddd, *J*=12.6, 9.1, 7.1 Hz, 1 H), 1.56- 1.44 (m, 1 H).

MS (TSP) *m/z* (M+1) : 374.

Example 186

(3*S*)-3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)-4-cyanobutanamide

(3*S*)-5-amino-3-[(*tert*-butoxycarbonyl)amino]-5-oxopentanoic acid (57 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (142mg, 0.375 mmol) were diluted in 4 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (64 mg, 87μL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (65 mg, 0.25 mmol) in dry *N, N*-dimethylformamide (1mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was diluted in dichloromethane (5 mL) and trifluoroacetic acid (1 mL) was added. After 15h stirring, the solvent were evaporated under vacuum. The crude material was diluted in ethyl acetate and washed 3 times with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by HPLC : column : XTerra® prep MSC$_8$, gradient 20-80%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 12% (11 mg). ^{1}H NMR (400 MHz, MeOD-d$_4$) :δ 8.44 (s, 1 H), 8.36 (dd, *J*=5.3, 0.8 Hz, 1 H), 8.18 (dd, *J*=5.5, 0.8 Hz, 1 H), 7.55 - 7.51 (m, 2 H), 7.36 (dd, *J*=5.3, 1.6 Hz, 1 H), 7.31 - 7.26 (m, 3 H), 7.09 (dd, *J*=1.6, 0.8 Hz, 1 H), 7.02 (dd, *J*=5.4, 1.7 Hz, 1 H), 6.99 - 6.94 (m, 1 H), 3.61 - 3.53 (m, 1 H), 2.73 - 2.63 (m, 4 H). ^{13}C NMR (101 MHz, MeOD-d$_4$) :δ 171.85 (s, 1 C), 158.52 (s, 1

C), 153.82 (s, 1 C), 149.88 (s, 1 C), 149.72 (s, 1 C), 149.39 (s, 1 C), 148.64 (s, 1 C), 142.40 (s, 1 C), 129.91 (s, 2 C), 123.02 (s, 1 C), 120.63 (s, 2 C), 119.00 (s, 1 C), 118.66 (s, 1 C), 113.34 (s, 1 C), 113.01 (s, 1 C), 109.09 (s, 1 C), 46.82 (s, 1 C), 43.47 (s, 1 C), 26.06 (s, 1 C).

MS (TSP) *m/z* (M+1): 373.

Example 187

N^1-(2'-anilino-4,4'-bipyridin-2-yl)cyclopropane-1,1-dicarboxamide

1-(aminocarbonyl)cyclopropanecarboxylic acid (32 mg, 0.25 mmol) and *N*-[(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylene]-*N*-methylmethanaminium hexafluorophosphate (142 mg, 0.375 mmol) were diluted in 4 mL of dry *N, N*-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (64 mg, 87µL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (65 mg, 0.25 mmol) in dry *N, N*-dimethylformamide (1mL) was slowly added and the mixture stirred for 15h at 20°C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 48 % (45 mg). 1H NMR (400 MHz, MeOD-d_4) :δ 8.43 (s, 1 H), 8.37 (d, *J*=5.1 Hz, 1 H), 8.19 (d, *J*=5.6 Hz, 1 H), 7.53 (d, *J*=7.6 Hz, 2 H), 7.41 - 7.36 (m, 1 H), 7.32 - 7.25 (m, 2 H), 7.09 (s, 1 H), 7.03 (d, *J*=7.1 Hz, 1 H), 7.00 - 6.94 (m, 1 H), 1.71 - 1.64 (m, 2 H), 1.57 - 1.48 (m, 2 H).

MS (TSP) *m/z* (M+1) : 374.

Example 188

(3*S*)-1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide

Ethyldiisopropylamine (129 mg, 1.0 mmol) was slowly added to a solution of N,N,N',N'-tetramethyl-o-(benzotriazol-1-yl)uronium tetrafluoroborate (321 mg, 1.0 mmol), hydroxybenzotriazole (137 mg, 1.0 mmol) and 1-acetylpiperidine-3-carboxylic acid (171 mg, 1.0 mmol) in 3 mL of DMF under nitrogen at 20 °C. After 5min, this solution was added to a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (200 mg, 0.76 mmol) in 2 mL of dimethylformamide under nitrogen. After 2 days of stirring, the reaction was quenched

with a 2M aqueous solution of potassium carbonate (5 mL). The aqueous layer was extracted with dichloromethane. After evaporation of the solvent, the resulting oil was purified by HPLC. Yield : 53 mg (17%). ^{1}H NMR (MeOD-d_4) :δ 8.52-8.42 (m, 2H), 7.95 (d, J = 6.5 Hz, 1H), 7.58 (m, 3H), 7.51-7.42 (m, 4H), 7.34 (dd, J = 7, 2 Hz, 1H), 4.53 (m, 1H), 4.19 (m, 1H), 3.98-3.84 (m, 2H), 2.99 (m, 1H), 2.13 (s, 3H), 2.13-1.26 (m, 4H).
MS (ES) *m/z* (M+1) : 416.

Example 189

***N*-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide** (+) and (-)

1-Hydroxybenzotriazole (104 mg, 0.76 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (244 mg, 0.76 mmol) and tetrahydrofuran-3-carboxylic acid (72μL, 0.76 mmol) were diluted in dry *N,N*-dimethylformamide (4 mL) under a nitrogen atmosphere. Diisopropylethylamine (264 μL, 1.52 mmol) was added dropwise. After 30 min stirring, a solution of *N*-phenyl-4,4'-bipyridine-2,2'-diamine (200 mg, 0.76 mmol) in dry *N,N*-dimethylformamide (2 mL) was slowly added and the solution was stirred for 3 days at room temperature. The reaction mixture was poured on a aqueous solution of potassium carbonate (2M, 10 mL) and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : gradient 100/0 to 90/10). Yield : 21 % (59 mg). The racemic mixture was separated by chiral chromatography to afford 10 mg of the (+) enantiomer and 10 mg of the (-) enantiomer.

^{1}H NMR (400 MHz, $CDCl_3$) :δ 10.56 (s, 1 H), 8.96 (s, 1 H), 8.45 (s, 1 H), 8.36 (d, *J*=5.6 Hz, 1 H), 8.01 (d, *J*=6.1 Hz, 1 H), 7.49 - 7.41 (m, 2 H), 7.37 - 7.30 (m, 3 H), 7.18 (s, 1 H), 7.12 (d, *J*=4.5 Hz, 1 H), 7.06 (d, *J*=6.1 Hz, 1 H), 4.05 - 3.95 (m, 3 H), 3.87 - 3.79 (m, 1 H), 3.25 - 3.16 (m, 1 H), 2.30 - 2.21 (m, 2 H).
MS (ES) *m/z* (M+1) : 361.

Example 190

***N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydrofuran-3-carboxamide**

1-Hydroxybenzotriazole (51 mg, 0.38 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (122 mg, 0.38 mmol) and tetrahydrofuran-3-

carboxylic acid (24µL, 0.25 mmol) were diluted in dry *N,N*-dimethylformamide (3 mL) under a nitrogen atmosphere. Diisopropylethylamine (87 µL, 0.50 mmol) was added dropwise. After 30 min stirring, a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (70 mg, 0.25 mmol) in dry *N,N*-dimethylformamide (2 mL) was slowly added and the solution was stirred for 3 days at room temperature. The reaction mixture was poured on a saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 32 % (30 mg). The racemic mixture was separated by chiral chromatography to afford 10 mg of the (-) enantiomer and 12 mg of the (+) enantiomer.^{1}H NMR (400 MHz, MeOD-d_4) :δ 8.37 (s, 1 H), 8.32 (d, *J*=5.1 Hz, 1 H), 8.12 (d, *J*=5.1 Hz, 1 H), 7.49 (dd, *J*=9.1, 4.5 Hz, 2 H), 7.31 (d, *J*=5.1 Hz, 1 H), 7.00 - 6.94 (m, 4 H), 3.97 (t, *J*=8.1 Hz, 1 H), 3.92 - 3.85 (m, 2 H), 3.81 - 3.71 (m, 1 H), 2.18 (q, *J*=7.1 Hz, 2 H). ^{19}F NMR (376 MHz, MeOD-d_4) :δ -124.05 (m, 1 F).
MS (ES) *m/z* (M+1) : 379.

Example 191

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydro-2*H*-pyran-4-carboxamide

Tetrahydro-2*H*-pyran-4-carboxylic acid (97.5 mg, 0.75 mmol) was dissolved in 5 mL of thionyl chloride and the solution stirred for 30 min at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 2 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (70 mg, 0.25 mmol) in 10 mL of pyridine. After 1h stirring, the solvent was removed under vacuum and the crude product was purified by HPLC column : XTerra® prep MSC$_8$, gradient 20-80%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 47% (130 mg). ^{1}H NMR (400 MHz, DMSO-d_6) :δ 10.63 (s, 1 H), 9.31 (s, 1H), 8.49 (s, 1 H), 8.43 (d, *J*=5.1 Hz, 1 H), 8.25 (d, *J*=5.6 Hz, 1 H), 7.76 - 7.69 (m, 2 H), 7.45 - 7.40 (m, 1 H), 7.14 - 7.06 (m, 4 H), 3.94 - 3.87 (m, 2 H), 2.83 - 2.73 (m, 1 H), 1.74 - 1.64 (m, 4 H).
MS (TSP) *m/z* (M+1) : 393.

Example 192

Ethyl 4-({2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoate

4-Ethoxy-4-oxobutanoic acid (95 mg, 0.65 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (342 mg, 0.90 mmol) were diluted in 6 mL of dry N,N-dimethylformamide under a nitrogen atmosphere. Diisopropylethylamine (74 mg, 100uL, 0.575 mmol) was added dropwise. After 1h stirring, a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (140 mg, 0.50 mmol) in dry N,N-dimethylformamide (2mL) was slowly added and the mixture stirred for 15h at 20 C. The mixture was poured on a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford a crude product which was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 35 % (72 mg). ^{1}H NMR (400 MHz, DMSO- d_6) :δ 10.71 (s, 1 H), 9.31 (s, 1 H), 8.46 - 8.37 (m, 2 H), 8.25 (d, *J*=5.6 Hz, 1 H), 7.72 (dd, *J*=9.1, 5.1 Hz, 2 H), 7.47 - 7.37 (m, 1 H), 7.14 - 7.04 (m, 4 H), 4.08 - 3.98 (m, 2 H), 2.71 (d, *J*=7.1 Hz, 2 H), 2.60 (d, *J*=7.1 Hz, 2 H), 1.19 - 1.11 (m, 3 H).

MS (TSP) *m/z* (M+1) : 409.

Example 193

4-({2'-[(4-Fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoic acid

Ethyl 4-({2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoate (50 mg, 0.12 mmol) was diluted in a mixture of ethanol/water/THF (5/5/3 mL). 2 mL of a 2M aqueous solution of sodium hydroxide were added and the reaction mixture was stirred for 1h at room temperature. The solution was concentrated under vacuum, filtered and the filtrate was extracted with ethyl acetate. The aqueous layer was acidified with acetic acid to pH 4 and then extracted with ethyl acetate (3x10 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum to afford the acid. Yield : 88% (40 mg). 1H NMR (400 MHz, DMSO- d_6) :δ11.14 (s, 1 H), 9.34 (s, 1 H), 8.46 (s, 1 H), 8.44 - 8.37 (m, 1 H), 8.24 (d, *J*=5.3 Hz, 1 H), 7.78 - 7.67 (m, 2 H), 7.38 (dd, *J*=5.2, 1.7 Hz, 1 H), 7.15 - 7.04 (m, 4 H), 2.65 - 2.56 (m, 2 H), 2.46 - 2.37 (m, 2 H).

MS (TSP) *m/z* (M+1) : 381.

Example 194

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-3-(methylthio)propanamide

3-(Methylthio)propanoic acid (21 mL, 24 mg, 0.25 mmol) was slowly added to 1 mL of a 1M oxalyl chloride solution in dichloromethane under nitrogen atmosphere at 0°C. After 30 min stirring, the solvent was removed under vacuum and the afforded oil was diluted in 0.5 mL of dry dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (70 mg, 0.25 mmol) in pyridine (5mL). After 1h stirring at 20°C, the mixture was filtered and the solvent evaporated under vacuum. The crude material was purified by flash chromatography (ethyl acetate/ethanol . 98/2). Yield : 38% (36 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.46 (s, 1 H), 8.34 - 8.30 (m, 1 H), 8.26 (d, *J*=5.3 Hz, 1 H), 8.24 (s, 1 H), 7.40 - 7.34 (m, 2 H), 7.20 (dd, *J*=5.2, 1.7 Hz, 1 H), 7.09 - 7.02 (m, 2 H), 6.98 (dd, *J*=5.3, 1.6 Hz, 1 H), 6.92 (s, 1 H), 6.55 (s, 1 H), 2.89 (t, *J*=6.8 Hz, 2 H), 2.72 (t, *J*=6.9 Hz, 2 H), 2.17 (s, 3 H).

MS (TSP) *m/z* (M+1) : 383.

Example 195

(±)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide

(±)-1-Acetylpiperidine-3-carboxylic acid (85 mg, 0.5 mmol) was dissolved in 3 mL of thionyl chloride and the solution was stirred for 1h at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 1.0 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (140 mg, 0.5 mmol) in 7 mL of pyridine. After 10 min stirring, the solvent was removed under vacuum and the crude product was purified by flash chromatography (ethyl acetate/methanol : 95/5 to 90/10). Yield : 17% (38 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.86 (s, 1 H), 8.44 (s, 1 H), 8.33 - 8.28 (m, 1 H), 8.26 - 8.21 (m, 1 H), 7.40 - 7.34 (m, 2 H), 7.23 - 7.15 (m, 1 H), 7.07 - 7.01 (m, 2 H), 6.96 (m, 2 H), 6.92 (s, 1 H), 4.60-4.50 (m, 1 H), 3.95-3.70 (m, 1 H), 3.42 – 2.70 (m, 2 H), 2.58-2.52 (m, 1 H), 2.14 - 2.06 (m, 4 H), 2.00-1.80 (m, 2 H), 1.52 (m, 1 H).

MS (TSP) *m/z* (M+1): 434.

Example 196

(3*R*)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide

(3*R*)-1-acetylpiperidine-3-carboxylic acid (75 mg, 0.44 mmol) was dissolved in 5 mL of thionyl chloride and the solution was stirred for 1h at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 1.5 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (115 mg, 0.41 mmol) in 5 mL of pyridine. After 10 min stirring, the solvent was removed under vacuum and the crude product was purified by HPLC column : XTerra® prep MSC$_8$, gradient 20-60%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 46% (82 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.86 (s, 1 H), 8.44 (s, 1 H), 8.33 - 8.28 (m, 1 H), 8.26 - 8.21 (m, 1 H), 7.40 - 7.34 (m, 2 H), 7.23 - 7.15 (m, 1 H), 7.07 - 7.01 (m, 2 H), 6.96 (m, 2 H), 6.92 (s, 1 H), 4.60-4.50 (m, 1 H), 3.95-3.70 (m, 1 H), 3.42 – 2.70 (m, 2 H), 2.58-2.52 (m, 1 H), 2.14 - 2.06 (m, 4 H), 2.00-1.80 (m, 2 H), 1.52 (m, 1 H).

MS (TSP) *m/z* (M+1): 434.

<u>Example 197</u>

(3*S*)-1-acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide

(3*S*)-1-acetylpiperidine-3-carboxylic acid (75 mg, 0.44 mmol) was dissolved in 5 mL of thionyl chloride and the solution was stirred for 1h at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 1.5 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (115 mg, 0.41 mmol) in 5 mL of pyridine. After 10 min stirring, the solvent was removed under vacuum and the crude product was purified by HPLC column : XTerra® prep MSC$_8$, gradient 20-60%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 58% (102 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.86 (s, 1 H), 8.44 (s, 1 H), 8.33 - 8.28 (m, 1 H), 8.26 - 8.21 (m, 1 H), 7.40 - 7.34 (m, 2 H), 7.23 - 7.15 (m, 1 H), 7.07 - 7.01 (m, 2 H), 6.96 (m, 2 H), 6.92 (s, 1 H), 4.60-4.50 (m, 1 H), 3.95-3.70 (m, 1 H), 3.42 – 2.70 (m, 2 H), 2.58-2.52 (m, 1 H), 2.14 - 2.06 (m, 4 H), 2.00-1.80 (m, 2 H), 1.52 (m, 1 H).

MS (TSP) *m/z* (M+1): 434.

Example 198

1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}pyrrolidine-3-carboxamide (E1) and (E2)

1-Acetylpyrrolidine-3-carboxylic acid (97 mg, 0.62 mmol) was dissolved in 5 mL of thionyl chloride and the solution was stirred for 1h at room temperature. The solvent was removed under vacuum and the resulting oil was dissolved in 1.5 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (141 mg, 0.51 mmol) in 5 mL of pyridine. After 1h stirring, the solvent was removed under vacuum and the crude product was purified by HPLC : XTerra® prep MSC$_8$, gradient 20-50%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 37% (80 mg). This racemate was then purified on a chiral column to afford 2 enantiomers E1 (6 mg) and E2 (6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.67 - 8.58 (m, 1 H), 8.49 - 8.40 (m, 1 H), 8.34 - 8.28 (m, 1 H), 8.28 - 8.20 (m, 1 H), 7.41 - 7.34 (m, 2 H), 7.25 - 7.18 (m, 1 H), 7.09 - 7.02 (m, 2 H), 6.99 - 6.95 (m, 1 H), 6.95 - 6.87 (m, 2 H), 3.87-3.73 (m, 3 H), 3.57 - 3.47 (m, 1 H), 3.26 - 3.04 (m, 1 H), 2.44 - 2.23 (m, 2 H), 2.09 - 2.05 (m, 3 H).

MS (TSP) *m/z* (M+1) : 420.

Example 199

3-(Aminosulfonyl)-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}benzamide

3-(Aminosulfonyl)benzoic acid (56 mg, 0.28 mmol) was diluted in thionyl chloride (5 mL) and the mixture was heated at reflux for 4h. The solvent was evaporated and the crude material dissolved in 1 mL dichloromethane. This solution was added dropwise to a solution of *N*-(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine (77 mg, 0.27 mmol) in 5 mL of pyridine. After 2h stirring, the resulting mixture was concentrated in vacuo and the crude material purified by HPLC : XTerra® prep MSC$_8$, gradient 20-80%B, 20mL/min, 40°C, (A-0.1M NH_4OAc in 0.1% CH_3CN aqueous solution, B-CH_3CN). Yield : 1.5% (2 mg).^{1}H NMR (400 MHz, MeOD-d$_4$) : δ 8.58 (s, 1 H), 8.51 (s, 1 H), 8.47 (d, *J*=5.3 Hz, 1 H), 8.23 - 8.17 (m, 2 H), 8.13 (d, *J*=8.4 Hz, 1 H), 7.73 (t, *J*=7.8 Hz, 1 H), 7.60 - 7.52 (m, 2 H), 7.47 (dd, *J*=5.2, 1.5 Hz, 1 H), 7.11 - 7.00 (m, 4 H).

MS (TSP) *m/z* (M+1): 464.

Example 200

Ethyl 2-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylate

N-phenyl-4,4'-bipyridine-2,2'-diamine (131 mg, 0.50 mmol) was dissolved in 5 mL of methanol and 2-formylcyclopropanecarboxylic acid ethyl ester (85 mg, 0.60 mmol) was added. After cooling at 0°C, acetic acid was added until pH 4 and the reaction was stirred for 15 min at this temperature. Then sodium cyanoborohydride (38 mg, 0.60 mmol) was added and the mixture was allowed to warm to room temperature and the reaction was followed by TLC until completion. The solution was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The crude product was purified by flash chromatography (ethyl acetate/methanol : 98/2). Yield : 62% (120 mg) as a yellow powder. ^{1}H NMR (400 MHz, MeOD-d_4) : δ 8.10 (d, *J*=5.6 Hz, 1 H), 7.95 (t, *J*=5.6 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 2 H), 7.26 - 7.21 (m, 2 H), 6.98 (s, 1 H), 6.94 - 6.90 (m, 2 H), 6.75 - 6.70 (m, 2 H), 4.04 (q, *J*=7.1 Hz, 2 H), 3.56-3.19 (m, 2 H), 1.70 - 1.64 (m, 1 H), 1.61 - 1.53 (m, 1 H), 1.21 - 1.15 (m, 3 H), 1.13 - 1.07 (m, 1 H), 0.92 - 0.84 (m, 1 H).

MS (ES) *m/z* (M+1) : 389.

Example 201

2-{[(2'-Anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylic acid

Ethyl 2-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylate (120 mg, 0.31 mmol) was dissolved in a mixture of THF/H2O (2:1) (6mL). Then, potassium hydroxide (21 mg, 0.37 mmol) was added and the mixture stirred for 20h at 20°C. THF was evaporated and the aqueous layer extracted with ethyl acetate (2x10 mL). The aqueous layer was diluted (with 5 mL H_2O) and acidified with acetic acid until pH 5. The acidic mixture was extracted with ethyl acetate (2x10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford the acid as a pure product. Yield : 54% (60 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.18 (d, *J*=5.6 Hz, 1 H), 7.98 (d, *J*=5.6 Hz, 1 H), 7.61 (s, 1 H), 7.39 - 7.30 (m, 4 H), 7.11 - 7.03 (m, 2 H), 6.88 (d, *J*=4.0 Hz, 1 H), 6.71 (d, *J*=5.6 Hz, 1 H), 6.52 (s, 1 H), 3.50 (dd, *J*=13.1, 6.1 Hz, 1 H), 3.00 - 2.90 (m, 1 H), 1.78 (d, *J*=6.1 Hz, 1 H), 1.66 - 1.55 (m, 1 H), 1.37 - 1.28 (m, 1 H), 0.92 - 0.85 (m, 1 H).

MS (TSP) *m/z* (M+1) : 361.

Example 202

N-phenyl-*N'*-(tetrahydro-2*H*-pyran-4-ylmethyl)-4,4'-bipyridine-2,2'-diamine

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide (59 mg, 0.157 mmol) was dissolved in THF (5 mL) under N_2 atmosphere and the solution was cooled at 0°C. A solution of DIBAL 1M in hexane (2 ml, 2.0 mmol) was added dropwise and the solution was stirred at 25°C for 15h. H_2O (2 mL) was added and stirring continued for 30 min. The solution was filtered on a celite® pad and extracted with ethyl acetate. The organic layer was concentrated under vacuum and the crude material purified by HPLC. Yield : 71 % (40 mg). ^{1}H NMR (400 MHz, $CDCl_3$) :δ 8.22 (d, *J*=5.3 Hz, 1 H), 8.08 (d, *J*=5.3 Hz, 1 H), 7.37 - 7.27 (m, 5 H), 7.11 - 7.02 (m, 2 H), 6.90 (d, *J*=5.3 Hz, 1 H), 6.71 (d, *J*=5.3 Hz, 1 H), 6.48 (s, 1 H), 5.24 (s, 1 H), 3.98 (dd, *J*=11.1, 3.5 Hz, 2 H), 3.42 - 3.33 (m, 2 H), 3.20 (d, *J*=3.5 Hz, 2 H), 1.91 - 1.80 (m, 1 H), 1.70 (dd, *J*=13.0, 1.9 Hz, 2 H), 1.36 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) :δ 159.20 (s, 1 C), 156.67 (s, 1 C), 148.70 (s, 1 C), 148.61 (s, 1 C), 148.28 (s, 1 C), 148.15 (s, 1 C), 140.09 (s, 1 C), 129.41 (s, 2 C), 123.25 (s, 1 C), 120.68 (s, 2 C), 113.03 (s, 1 C), 110.85 (s, 1 C), 105.70 (s, 1 C), 104.11 (s, 1 C), 67.65 (s, 2 C), 48.14 (s, 1 C), 35.07 (s, 1 C), 30.88 (s, 2 C).

MS (ES) *m/z* (M+1) : 361.

Example 203

N-phenyl-*N'*-(tetrahydrofuran-3-ylmethyl)-4,4'-bipyridine-2,2'-diamine

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide (43 mg, 0.12 mmol) was dissolved in THF (5 mL) under N_2 atmosphere and the solution was cooled at 0°C. A solution of DIBAL 1M in hexane (2 ml, 2.0 mmol) was added dropwise and the solution was stirred at 25°C for 15h. H_2O (2 mL) was added and stirring continued for 30 min. The solution was filtered on a celite pad and extracted with ethyl acetate. The organic layer was concentrated under vacuum and the crude material purified by HPLC. The product was treated with 1 eq. HCl (aq.) and freeze dried to give the HCl salt. Yield : 61% (28 mg). ^{1}H NMR (400 MHz, MeOD-d_4) :δ 8.16 (d, *J*=5.6 Hz, 1 H), 7.90 (d, *J*=6.6 Hz, 1 H), 7.47 (d, *J*=8.6 Hz, 2 H), 7.32 - 7.24 (m, 2 H), 7.10 (s, 1 H), 7.06 -6.97 (m, 3 H), 3.91 - 3.80 (m, 2

H), 3.77 - 3.68 (m, 1 H), 3.57 (dd, *J*=8.6, 5.1 Hz, 1 H), 3.33 (d, *J*=7.6 Hz, 2 H), 2.60 (s, 1 H), 2.12 (d, *J*=13.1 Hz, 1 H), 1.68 (s, 1 H).
MS (ES) *m/z* (M+1) : 347.

List of abbreviations

SPA	**scintillation proximity assay**
ATP	**adenosine triphosphate**
ATF	**Activating transcription factor**
MOPS	**3-[*N*-Morpholino]-propanesulfonic acid**
EGTA	**Ethylene glycol-bis(β-aminoethylether)-*N,N,N',N'*-tetraacetic acid**
DTT	**dithiothreitol**
JNK	**Jun N-terminal kinases**
MAP	**mitogen-activated protein**

Biological evaluation

The compounds of this invention may be assayed for their activity according to the following procedure:

A scintillation proximity assay (SPA) based on the inhibition of JNK3 catalyzed transfer of the γ-phosphate group of [γ-^{33}P] ATP to biotinylated ATF2, has been set up to identify inhibitory compounds. The resulting ^{33}P-labeled biotinylated ATF2 is trapped on SPA beads surface coated with streptavidin.

The assay is performed in 96-well plates. Test compounds made up at 10 mM in DMSO and 1:3 serial dilutions are made in 100% DMSO. These serial dilutions are then diluted 1:10 in assay buffer (50 mM MOPS pH 7.2, 150 mM, NaCl, 0.1 mM EGTA, 1 mM DTT, 6.25 mM β-glycerolphosphate) and 10 µl are transferred to assay plates (results in 2% DMSO final concentration in assay). To each well with test compound a 2.4 µl JNK3/ATP enzyme solution (1.18 U/ml JNK3, 20 µM ATP, 2 mM $Mg(Ac)_2$, 0.01 % Brij-35 in assay buffer) was added. The mixture was pre-incubated for 10 minutes at ambient temperature. After this, 3.6 µl of a [γ-^{33}P] ATP-solution (0.20 µCi/µl [γ-^{33}P]ATP, 66.6 mM $Mg(Ac)_2$, 1 mM DTT, 50 mM MOPS pH 7.2, 150 mM NaCl, 0.1 mM EGTA) was added to each well followed by 10 µl a ATF2 solution (60 µg/ml biotinylated ATF2 in assay buffer) to start the reaction. The reaction was allowed to proceed for 10 minutes at ambient temperature. After this, the reaction was terminated by the addition of 200 µl per well of stop buffer/bead mix (0.4 mg/ml streptavidin coated SPA-beads in 50 mM EDTA, pH 7.6). Plates were sealed with a plastic cover and centrifuged (2000 rpm, 5 minutes) to settle the beads followed by counting in a Wallac 1450 microbeta™.

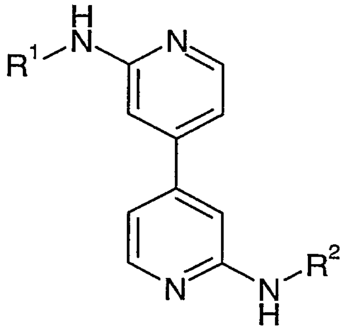
The IC_{50} values were calculated as the concentration of test compound at which the ATF2 phosphorylation is reduced to 50% of the control value.

Results

Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.001 nM to about 300 nM.

CLAIMS

1. A compound of the general Formula I



(I)

wherein:

R^1 is aryl or heteroaryl, each of which is optionally substituted with one or more of R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halogeno and NO_2;

R^2 is R^5, R^6, COR^5, COR^6, $CONHR^5$, $CONHR^6$, $CON(R^6)_2$, $COOR^5$, $COOR^6$, SO_2R^5 or SO_2R^6;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} trifluoroalkoxyl;

R^5 is aryl or heteroaryl, each of which is optionally substituted with one or more of R^7, OR^7, $OCOR^7$, $COOR^7$, COR^7, $CONR^7R^8$, $CONHOR^7$, $NHCOR^7$, NR^7R^8, $NHSO_2R^7$, SO_2R^7, $SO_2NR^7R^8$, SR^7, R^7SR^8, CN, halogeno, oxygen and NO_2;

R^6 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, heteroarylC_{1-6} alkyl, arylC_{1-6} alkyl, C_{1-6} alkoxyl, or C_{2-6} alkenyl, wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, heteroarylC_{1-6} alkyl, arylC_{1-6} alkyl, C_{1-6} alkoxyl and C_{2-6} alkenyl is optionally substituted with one or more A;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heteroarylC_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, aryl, C_{1-6} fluoroalkyl and C_{1-6} chloroalkyl,wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heteroaryl, heteroarylC_{1-6} alkyl, heterocycle and heterocycleC_{1-6} alkyl is optionally substituted with one or more B;

R^9 and R^{10} are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heterocycle, heterocycleC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6} alkyl, aryl or arylC_{1-6} alkyl, wherein any of C_{1-6} alkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, C_{2-6} alkenyl, heterocycle, heterocycleC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6} alkyl, aryl or arylC_{1-6} alkyl is optionally substituted with one or more B;

A is R^9, OR^9, $OCOR^9$, $COOR^9$, COR^9, $CONR^9R^{10}$, $CONHOR^9$, $NHCOR^9$, NR^9R^{10}, $NR^9SO_2R^{10}$, SO_2R^9, $SO_2NR^9R^{10}$, SR^9, R^9SR^{10} ,CN or halogeno;

B is C_{1-6} alkyl, C_{1-6} alkoxyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino or halogeno;

as a free base or a salt, solvate or solvate of salt thereof.

2. A compound according to claim 1, wherein
R^1 is aryl or heteroaryl, optionally substituted with one or more of R^3, OR^3, NR^3R^4, halogeno or NO_2;

R^2 is R^5, R^6, COR^5, COR^6, $CONHR^5$, $CONHR^6$, $COOR^6$ or SO_2R^6;

R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl or C_{1-6} fluoroalkyl;

R^5 is aryl or heteroaryl each of which is optionally substituted with one or more of R^7, OR^7, $COOR^7$, COR^7, $CONHOR^7$, NR^7R^8, SO_2R^7, $SO_2NR^7R^8$, SR^7, halogeno, oxygen and NO_2;

R^6 is hydrogen, C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, wherein any of C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl or heterocycle is optionally substituted with one or more A;

R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocycle,wherein any of C_{1-6} alkyl is optionally substituted with one or more B;

R^9 and R^{10} are each independently hydrogen, or C_{1-6} alkyl, wherein any C_{1-6} alkyl is optionally substituted with one or more B;

A is $COOR^9$, COR^9, $CONR^9R^{10}$, $NHCOR^9$, NR^9R^{10}, SR^9, R^9SR^{10} , or CN;

B is halogeno or di(C_{1-6} alkyl)amino.

3. A compound according to claim 1 or 2, wherein R^1 is aryl optionally substituted with one or more of R^3, OR^3 and NR^3R^4.

4. A compound according to claim 3, wherein said aryl is phenyl.

5. A compound according to claim 3 or 4, wherein R^3 is selected from C_{1-6} fluoroalkyl, methyl and halogeno.

6. A compound according to any one of claims 1 to 5, wherein R^2 is selected from R^5, COR^5 and $CONHR^5$.

7. A compound according to claim 6, wherein R^5 is aryl, optionally substituted with one or more of R^7, OR^7, $COOR^7$, COR^7, $CONHOR^7$, NR^7R^8, SO_2R^7, $SO_2NR^7R^8$, SR^7, halogeno, oxygen and NO_2.

8. A compound according to claim 7, wherein R^7 and R^8 are each independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocycle, wherein C_{1-6} alkyl is optionally substituted with one or more B, said B being halogeno.

9. A compound according to any one of claims 1 to 5, wherein R^2 is selected from R^6, COR^6, $CONHR^6$ and SO_2R^6.

10. A compound according to claim 9, wherein R^6 is selected from hydrogen, C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, heterocycleC_{1-6} alkyl, wherein any of C_{1-6} alkyl, (C_{3-8} cycloalkyl)C_{1-6} alkyl and heterocycle is optionally substituted with one or more A.

11. A compound according to claim 9, wherein said A is selected from $COOR^9$, COR^9, $CONR^9R^{10}$, $NHCOR^9$, NR^9R^{10}, SR^9, R^9SR^{10} and CN; and R^9 and R^{10} are each independently hydrogen or C_{1-6} alkyl.

12. A compound which is
N,N'-Bis[4-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(4-fluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(3,4-difluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis[3-(trifluoromethyl)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis[3-(trifluoromethoxy)phenyl]-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-fluorophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-methylphenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-aminophenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-methoxyphenyl)-4,4'-bipyridine-2,2'-diamine;
N,N'-Bis(2-ethoxyphenyl)-4,4'-bipyridine-2,2'-diamine;
N-(2'-anilino-4,4'-bipyridin-2-yl)-*trans*-4-methoxycyclohexanecarboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-*cis*-4-methoxycyclohexanecarboxamide;
N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*trans*-4-methoxycyclohexanecarboxamide;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-*cis*-4-methoxy-cyclohexanecarboxamide;

N-(6-methylpyridin-2-yl)-*N*'-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-*N*'-pyridin-2-yl-4,4'-bipyridine-2,2'-diamine;

N-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-*N*'-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyridin-3-yl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyrimidin-2-yl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyrimidin-5-yl-4,4'-bipyridine-2,2'-diamine;

(2E)-1-{4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]phenyl}-3-(dimethylamino)prop-2-en-1-one;

4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-pyrrolidin-1-ylethyl)benzenesulfonamide;

4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-N-(2-morpholin-4-ylethyl)benzenesulfonamide;

N-{4-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl}-N'-phenyl-4,4'-bipyridine-2,2'-diamine;

N-phenyl-N'-pyridin-4-yl-4,4'-bipyridine-2,2'-diamine;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-piperidin-1-ylpropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1,2,3-thiadiazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)isoxazole-5-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyrazine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-imidazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxybenzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-bromo-2-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-(methylthio)nicotinamide;

Methyl 4-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}benzoate;

3-(acetylamino)-N-(2'-anilino-4,4'-bipyridin-2-yl)benzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-[(pyridin-2-ylthio)methyl]-2-furamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide 1-oxide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-hydroxypyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-6-bromopyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)isonicotinamide 1-oxide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-hydroxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-6-hydroxypyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-benzoylpyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-6-methylpyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3,5-dimethylisoxazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-methoxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methyl-1,2,3-thiadiazole-5-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloroisonicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylisoxazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methylisoxazole-4-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1-methyl-1H-pyrrole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-chloronicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-chloro-1H-indole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-chloro-1H-pyrazole-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methyl-1H-pyrazole-3-carboxamide;

(2E)-N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(3-furyl)acrylamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(2-oxo-1,3-benzoxazol-3(2H)-yl)propanamide;

N'-(2'-anilino-4,4'-bipyridin-2-yl)-N,N-dimethylsuccinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2-[(4-chlorophenyl)sulfonyl]acetamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-methoxycyclohexanecarboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-methoxypropanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)butanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)nicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-4-(dimethylamino)benzamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-2,6-dimethoxynicotinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-1H-indole-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-5-methylpyrazine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)pyridine-2-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-furamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-*N*'-phenylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-phenylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[1-(4-bromophenyl)ethyl]urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-thien-3-ylurea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-fluorophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(chloromethyl)phenyl]urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-cyanophenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dimethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dimethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-ethylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxyphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-fluoro-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-fluorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-difluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-difluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorobenzyl)urea;
N-(4-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea;
N-(3-acetylphenyl)-N'-(2'-anilino-4,4'-bipyridin-2-yl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-isopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-ethyl-6-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-mesitylurea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-propylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(dimethylamino)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-1,3-benzodioxol-5-ylurea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxy-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methoxy-5-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-ethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methoxybenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-nitrophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-nitrophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(methylthio)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(methylthio)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-methylbenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chloro-5-methylphenyl)urea;

N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-chlorobenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-fluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3,4-trifluorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-isopropyl-6-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2-tert-butylphenyl)urea;
methyl 4-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)benzoate;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dimethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dimethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3-chloro-4-methoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[2-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[4-(trifluoromethyl)phenyl]urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,5-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,5-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(3,4-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,3-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,4-dichlorophenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-bromo-3-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-dichloropyridin-4-yl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butyl-2-methylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[5-methyl-2-(trifluoromethyl)-3-furyl]urea;
ethyl 3-({[(2'-anilino-4,4'-bipyridin-2-yl)amino]carbonyl}amino)benzoate;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-butoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(2,6-diisopropylphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(4-methylbenzyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-{4-[(trifluoromethyl)thio]phenyl}urea;
N-(2'-anilino-4,4'-bipyridin-2-yl)-N'-[3,5-bis(trifluoromethyl)phenyl]urea;
1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide;
N-(2'-anilino-4,4'-bipyridin-2-yl)-5-oxoprolinamide;

N^3-acetyl-*N*^{1}-(2'-anilino-4,4'-bipyridin-2-yl)-β-alaninamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-4-carboxamide;

3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)butanamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)-L-prolinamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)acetamide;

Methyl 2'-anilino-4,4'-bipyridin-2-ylcarbamate;

N-(2'-anilino-4,4'-bipyridin-2-yl)methanesulfonamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)cyclohexanecarboxamide;

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-2-carboxamide;

1-Acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide;

Ethyl 4-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-4-oxobutanoate;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-2-carboxamide;

(*S*)-3 *N*2-acetyl-*N*1-(2'-anilino-4,4'-bipyridin-2-yl)methioninamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

Ethyl 3-[(2'-anilino-4,4'-bipyridin-2-yl)amino]-3-oxopropanoate;

N-(2'-anilino-4,4'-bipyridin-2-yl)-3-(methylthio)propanamide;

(±)*N*-(2'-anilino-4,4'-bipyridin-2-yl)-2-pyrrolidin-2-ylacetamide;

(3*S*)-3-amino-*N*-(2'-anilino-4,4'-bipyridin-2-yl)-4-cyanobutanamide;

*N*1-(2'-anilino-4,4'-bipyridin-2-yl)cyclopropane-1,1-dicarboxamide;

(*3S*)-1-acetyl-*N*-(2'-anilino-4,4'-bipyridin-2-yl)piperidine-3-carboxamide;

N-(2'-anilino-4,4'-bipyridin-2-yl)tetrahydrofuran-3-carboxamide (+) and (-);

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydrofuran-3-carboxamide;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}tetrahydro-2*H*-pyran-4-carboxamide;

Ethyl 4-({2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoate;

4-({2'-[(4-Fluorophenyl)amino]-4,4'-bipyridin-2-yl}amino)-4-oxobutanoic acid;

N-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}-3-(methylthio)propanamide;

(*±*)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;

(3*R*)-1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;

(3*S*)-1-acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}piperidine-3-carboxamide;
1-Acetyl-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}pyrrolidine-3-carboxamide;
3-(Aminosulfonyl)-*N*-{2'-[(4-fluorophenyl)amino]-4,4'-bipyridin-2-yl}benzamide;
Ethyl 2-{[(2'-anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylate;
2-{[(2'-Anilino-4,4'-bipyridin-2-yl)amino]methyl}cyclopropanecarboxylic acid;
N-phenyl-*N*'-(tetrahydro-2*H*-pyran-4-ylmethyl)-4,4'-bipyridine-2,2'-diamine;
N-phenyl-*N*'-(tetrahydrofuran-3-ylmethyl)-4,4'-bipyridine-2,2'-diamine;

as a free base or a salt, solvate or solvate of salt thereof.

13. A compound according to any one of claims 1 to 12, in the form of a pharmaceutically acceptable salt.

14. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1 to 13 in association with pharmaceutically acceptable carriers or diluents.

15. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1 to 13 for use in the prevention and/or treatment of conditions associated with JNK activation.

16. A compound according to any one of claims 1 to 13 for use in therapy.

17. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the prevention and/or treatment of conditions associated with JNK activation.

18. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the prevention and/or treatment of conditions selected from: central or peripheral neurological degenerative disorders including Alzheimer's disease,

cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, epilepsy, a peripheral neuropathy, spinal cord injury, head trauma; autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, asthma, septic shock, transplant rejection; cardiovascular diseases including stroke, arterosclerosis, myocardial infarction, myocardial reperfusion injury; cancer including breast-, colorectal, pancreatic, prostate cancer.

19. The use according to claim 18 wherein said condition is Alzheimer's disease.

20. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the prevention and/or treatment of conditions associated with inhibiting the expression of inducible pro-inflammatory proteins.

21. Use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the prevention and/or treatment of conditions selected from edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain and arthritis pain.

22. A method of treating or preventing conditions associated with JNK activation comprising the administration of a therapeutically effective amount of a compound of Formula I according to any one of claims 1 to 13 to a mammal in need thereof.

23. A method of treating or preventing conditions selected from central or peripheral neurological degenerative disorders including Alzheimer's disease, cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease,

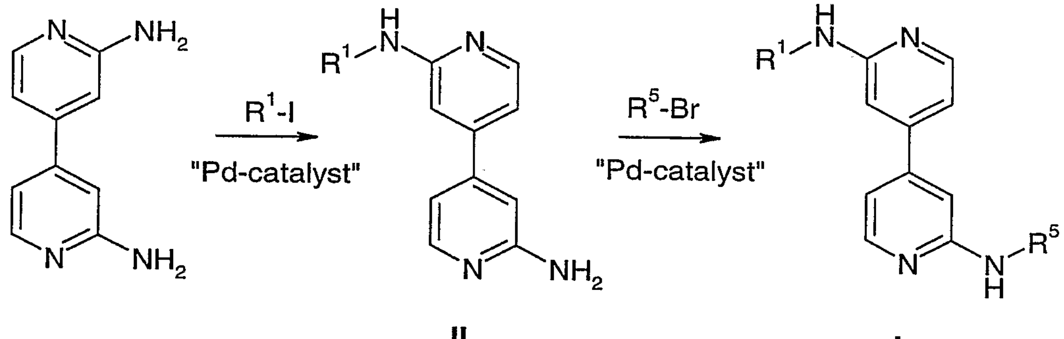
Niemann-Pick's Disease, epilepsy, a peripheral neuropathy, spinal cord injury, head trauma; autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease, Crohn's disease, rheumatoid arthritis, asthma, septic shock, transplant rejection; cardiovascular diseases including stroke, arterosclerosis, myocardial infarction, myocardial reperfusion injury; cancer including breast-, colorectal, pancreatic, prostate cancer comprising the administration of a therapeutically effective amount of a compound of Formula I according to any one of claims 1 to 13 to a mammal in need thereof.

24. The method according to claim 23, wherein said condition is Alzheimer's disease.

25. A method of treating or preventing associated with inhibiting the expression of inducible pro-inflammatory proteins comprising the administration of a therapeutically effective amount of a compound of Formula I according to any one of claims 1 to 13 to a mammal in need thereof.

26. The method according to claim 25, wherein the condition is selected from edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain and arthritis pain.

27. A process for the preparation of a compound of formula **Ia**, wherein R^1 and R^5 are as defined in claim 1;



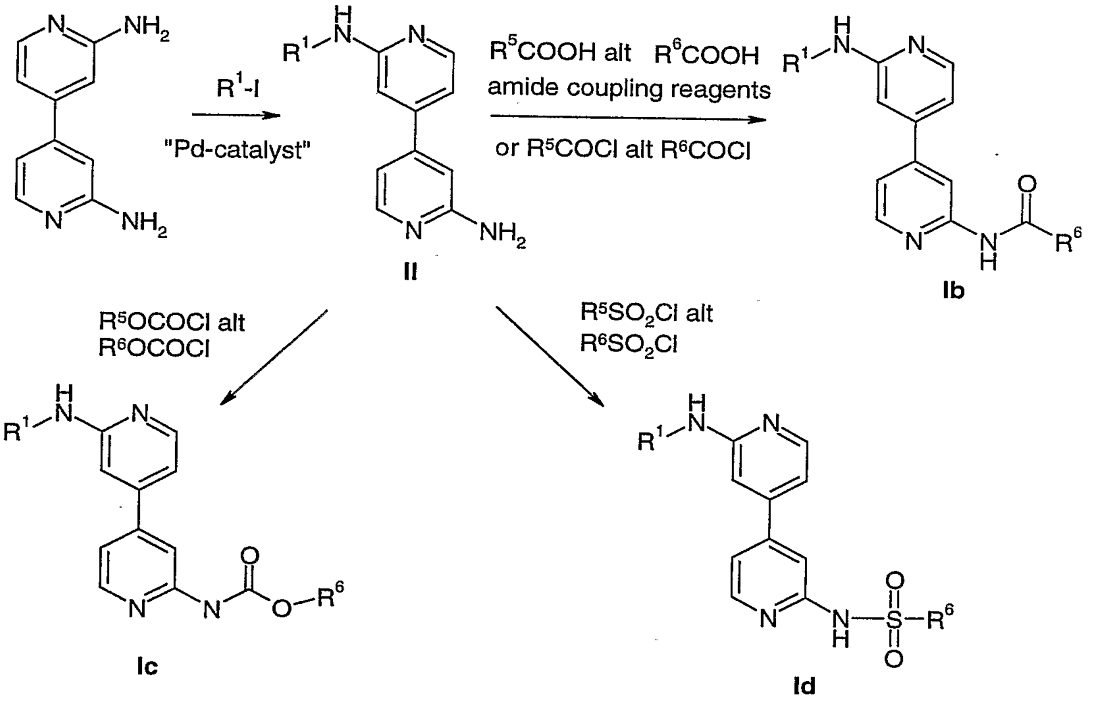
II **Ia**

comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and

reacting a compound of Formula **II** in a second arylation reaction with an arylhalide (R^5-Br) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") to obtain a compound of formula **Ia**.

28. A process for the preparation of a compound of formula **Ib**, **Ic** or **Id**, wherein R^1, R^5 and R^6 are as defined in claim 1;



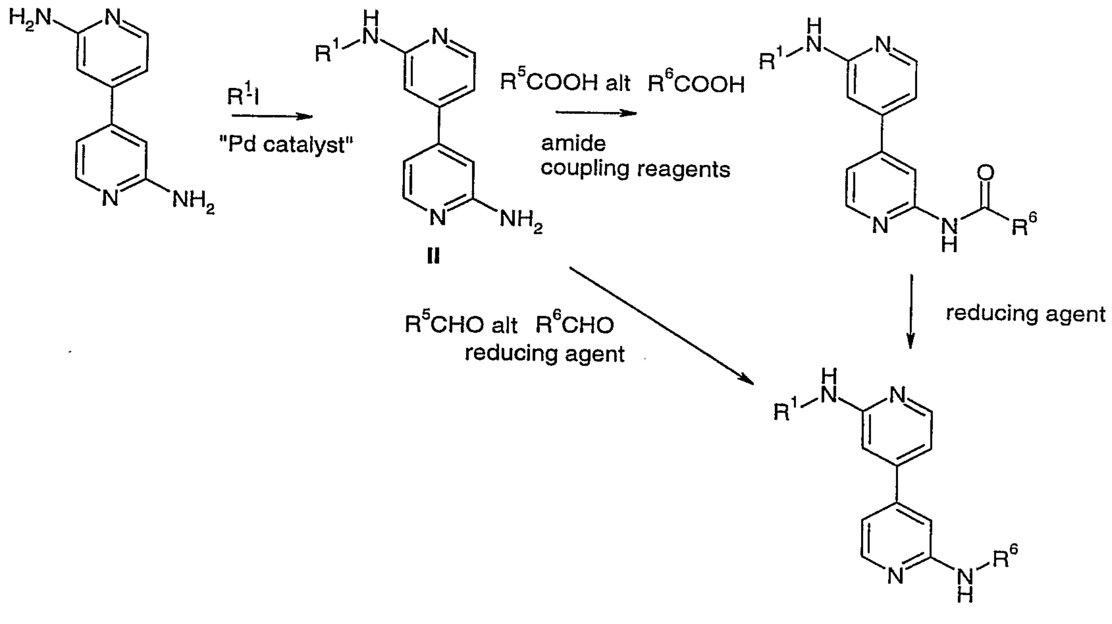
comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and reacting said compound of Formula **II** with a carboxylic acid (“R^5COOH alt R^6COOH”) in the presence of a amide coupling reagent and a base in an inert solvent to obtain a compound according to formula **Ib**; or

reacting said compound of Formula **II** with a carboxylic acid chloride (“R^5OCOCl alt R^6OCOCl”) in an inert solvent in the presence of a base in a solvent to obtain a compound according to formula **Ic**; or

reacting said compound of Formula **II** with a chlorocarbonate or sulfonylchloride (“R^5SO_2Cl or R^6SO_2Cl”) to obtain a compound according to formula **Id**.

29. A process for the preparation of a compound of formula **Ie**, wherein R^1, R^5 and R^6 are as defined in claim 1;



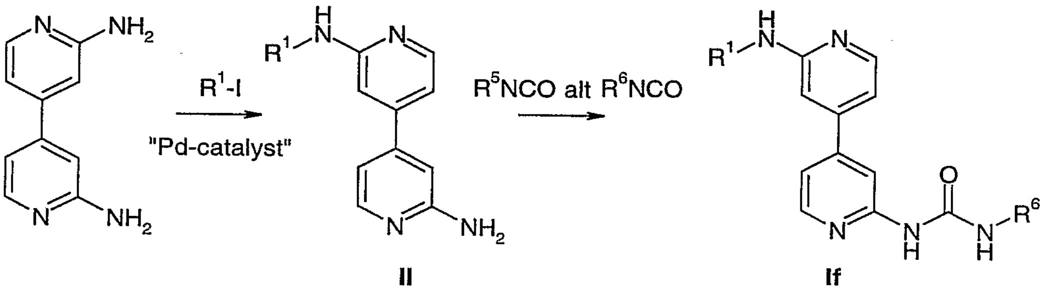
Ie

comprising the steps:

reacting 4.4’-bipyridine-2,2’-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst (“Pd-catalyst”) in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and reacting said compound of Formula **II** with a carboxylic acid ("R^5COOH alt R^6COOH") followed by reduction to the amine with a reducing agent in a solvent to obtain a compound according to formula **Ie**; or

reacting said compound of Formula **II** with a carboxaldehyde ("R^5CHO alt R^6CHO") in the presence of a reducing agent to obtain a compound according to formula **Ie**.

30. A process for the preparation of a compound of formula **If**, wherein R^1, R^5 and R^6 are as defined in claim 1;

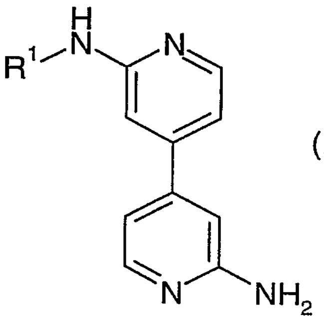


comprising the steps:

reacting 4.4'-bipyridine-2,2'-diamine with an arylhalide (R^1-I) and with a transition metal catalyst or a palladium catalyst ("Pd-catalyst") in the presence of a base in an ether or hydrocarbon solvent to give a compound according to Formula **II**; and

reacting said compound of Formula **II** with an isocyanate ("R^5NCO alt R^6NCO") in a solvent, to obtain a compound according to Formula **If**.

31. A compound according to formula II



(II)

wherein is R^1 is aryl or heteroaryl each of which is optionally substituted with one or more of the following R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halogeno or NO_2;

R^3 and R^4 are each independently hydrogen, halogeno, C_{1-6} alkyl, C_{1-6} alkyl optionally substituted by NR^3R^4, C_{3-8} cycloalkyl, C_{3-6} alkenyl, C_{3-6} alkenyl optionally substituted by NR^3R^4, (C_{3-8} cycloalkyl)C_{1-6} alkyl, heterocycle, hetrocycleC_{1-6} alkyl, C_{1-6} fluoroalkyl, or alternatively NR^3R^4 can form a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms being optionally substituted with one or more A;

A is C_{1-6} alkyl or halogeno;

as a free base or a salt, solvate or solvate of salt thereof.

32. A compound which is

N-Phenyl-4,4'-bipyridine-2,2'-diamine;

N-(4-Fluorophenyl)-4,4'-bipyridine-2,2'-diamine;

as a free base or a salt, solvate or solvate of salt thereof.

33. The use compound according to Formula II in claim 31 for the preparation of a compound of formula I as defined in any one of claims 1 to 13.

34. The use of a compound according to claim 32 for the preparation of a compound of formula I as defined in any one of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001911

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, C07D 401/14, A61K 31/444, A61P 25/00, A61P 35/00, A61P 9/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9932448 A1 (AMGEN INC.), 1 July 1999 (01.07.1999) --	1-34
X	WO 9732589 A1 (NOVARTIS AG), 12 Sept 1997 (12.09.1997) --	1-34
A	WO 0246184 A1 (VERTEX PHARAMCEUTICALS INCORPORATED), 13 June 2002 (13.06.2002) --	1-34
A	US 4004012 A (LESHER ET AL), 18 January 1977 (18.01.1977) -- --------	1-34

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 19 February 2004	Date of mailing of the international search report 26 -02- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer CAROLINA GÓMEZ LAGERLÖF/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/01911

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 22-26
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II.1

Claims 22-26 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

24/12/2003

International application No.
PCT/SE 2003/001911

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INTERNATIONAL SEARCH REPORT

Information on patent family members

24/12/2003

International application No.

PCT/SE 2003/001911

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Form PCT/ISA/210 (patent family annex) (January 2004)